THE RESILIENT STUDY: A RETROSPECTIVE, DESCRIPTIVE CORRELATIONAL INVESTIGATION OF RATE AND CORRELATES OF ORAL ENDOCRINE THERAPY ADHERENCE IN OLDER WOMEN WITH BREAST CANCER

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ABSTRACT

Breast cancer is the most prevalent and costly cancer among females. About 80% of breast cancer patients take oral endocrine therapy (OET), such as anastrozole, letrozole, tamoxifen, and exmestane. These medications increase survival, improve quality-of-life and decrease healthcare costs, yet many patients do not take it properly. The purpose of this study is to identify rates of and multi-level determinants influencing OET non-adherence (NA) among older women with breast cancer enrolled in Medicare Part-D. It is important to consider older women with breast cancer; the medium breast cancer patient age was 62 and more than 20% of newly diagnosed patients were older than 70 in 2021.

Most existing research on OET-NA has been conducted on small samples at single sites and has focused predominantly on patient issues rather than exploring multi-level determinants. Despite their unique needs due to aging effects, there are no specific guidelines or known OET-NA determinants for older women with breast cancer. To resolve this, I utilized a large data set with theoretical frameworks (World Health Organization's five-dimensional-model of factors and Bronfenbrenner's ecological system theory) to understand multi-level determinants through a secondary data analysis of the Surveillance-Epidemiology-End-Results Medicare database (average age 69). All women in the database

with a cancer diagnosis were identified using ICD-9 and ICD-10 codes in Medicare Part-D to identify ten years of OET-NA rates. I then focused on the most recently released data from 2019 to identify up-to-date trends in OET-NA determinants.

Results demonstrated that OET-NA was significantly affected by (a) patient-related factors of ethnicity and psychological issues, (b) socioeconomic-related factors of marital status, and lifestyle, (c) therapy-related factors of switching OET medications and increased number of drug therapy experiences, (d) condition-related factors of cancer stage and comorbidities, and (e) health care team/system-related factors of characteristics of healthcare team and system. The first steps in developing interventions for better nursing practice based on strong theoretical frameworks were determining rates and multi-level determinants of OET-NA on older women. This study can also support the implementation of better nursing policies to improve patient education and OET adherence— ultimately decreasing morbidity and mortality, and increasing quality-of-life.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Nursing and Health Studies, have examined a dissertation titled "The RESILIENT Study: A Retrospective, Descriptive, Correlational Investigation of Rate and Correlates of Oral Endocrine Therapy (OET) Adherence in Older Women with Breast Cancer," presented by Sunny Yoo Ruggeri, candidate for the Doctor of Philosophy degree and hereby certify that in their opinion it is worthy of acceptance.

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DEDICATION

I dedicate my dissertation work to my family, colleagues, and friends in their support of this dissertation. I give special thanks to my husband, Andrew Ruggeri for technical support and for being there for me throughout the entire doctorate program. I also give another special thank you to my daughter, Adaleine Giavana Ruggeri. You were always so cooperative and patient through this hard process. Lastly, I dedicate this work and give special thanks to Dr. Cynthia L. Russell for guiding my medication adherence research with her expertise.

CHAPTER 1

INTRODUCTION

The rates multilevel influences endocrine therapy (RESILIENT) study is a retrospective, descriptive, correlational investigation of rate and correlates of oral endocrine therapy non-adherence in older women with breast cancer.

Chapter one provides a general introduction and identification of the problems related to oral endocrine therapy (OET) non-adherence (NA) in older women with breast cancer within the current literature. In this chapter, I will review (a) aims, research questions and definitions; (b) description of the problem; (c) significance of the problem; (d) conceptual/theoretical framework; and (e) innovation of the RESILENT study.

Aims, Research Questions, and Definitions

The purpose of this study is to identify the rate of OET-NA and the multi-level determinants that contribute to OET-NA in women with breast cancer. The purpose of this study is not hypothesis testing; rather, the purpose is identifying the rate of OET-NA and exploring the multi-level determinants that are correlated with OET-NA. Understanding the role of multi-level determinants such as patient-related, socio-economic-related, therapy-related, condition-related, and healthcare team/system-related factors will provide a blueprint for tailored interventions specific to breast cancer patients prescribed OET. The study's specific aims are as follows.

Specific Aims

This study aims to measure OET-NA rates and identify the multi-level determinants related to OET-NA in women with breast cancer to improve adherence to OET. Improving

adherence may lead to enhanced quality-of-life (QOL) and decrease recurrence rates, mortality, and medical costs for women with breast cancer.

Research Questions

The research questions are as follows: (a) what is the rate of adherence to OET in women with breast cancer? and (b) what are the multi-level determinants influencing OET-NA in women with breast cancer?

Definitions and Terminologies

I will now introduce the definitions and terminologies of this study, including adherence (related terms: initiation, implementation, persistence), medical possession ratio (MPR), measures, OET, medication-NA (related terms: inconsistency, delayed initiation, or early discontinuation), older adults, and over-adherence.

Adherence. Adherence was first conceptualized as compliance in the late 1970s (Butow et al., 2010). Kyngäs et al. (2000) described compliance as comprising three elements: (a) self-care responsibilities, (b) role in the treatment process, and (c) collaboration with health care providers. Osterberg and Blaschke (2005) described compliance as the passive action of the patient following the health care provider's order. Virijens et al. (2012) demonstrated that the term concordance was originally used to describe the patient–prescriber relationship and was often incorrectly applied as a synonym for compliance. Hansen (2015b) found that adherence puts the patient in the role of an active participant. However, since 2003, adherence has become the term preferred by researchers due to its more positive, less paternalistic, implication (Hansen, 2015b).

Adherence was defined by the World Health Organization (WHO) in 2003 as "the extent to which a person's behavior […] taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (Sabaté, 2003, p. 3). Virijens et al. (2012) developed the Ascertaining Barriers to Compliance (ABC) taxonomy to define medication adherence as a sequence of steps a patient must undertake to be defined as "adherent to treatment": (a) initiation, (b) implementation, and (c) discontinuation.

Initiation. Vrijens et al. (2012) defined initiation as taking the first dose of a prescribed medication.

Implementation. Vrijens et al. (2012) defined implementation as the continual process of the medication regimen, which they describe as taking the correct number of medications until finishing the last dose. This means implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose.

Discontinuation. Vrijens et al. (2012) explained that discontinuation means the end of treatment without additional doses to be taken afterwards. Discontinuation occurs when the patient stops taking the prescribed medication for whatever reason(s).

Persistence. Vrijens et al. (2012) defined persistence as the the length of time between initiation and the last dose, which immediately precedes discontinuation. In other words, persistence is taking medication as long as it is prescribed (Ruddy et al., 2009).

Medication Non-adherence (NA). Vrijens et al. (2012) described non-adherence as any inconsistency of the regimen, delayed initiation, or early discontinuation before

treatments finish. Medication-NA can be intentional (when the patient decides not to take their medication for a variety of reasons) or unintentional (i.e., forgetting a dose or misunderstanding the directions) (Bosworth et al., 2006).

Measures. Newly developed tools allow precise measurement of MA. There are two ways to identify MA: (a) subjective and (b) objective measures (Brown & Bussell, 2011; Hansen, 2015a).

Subjective Measures. Subjective measures include collecting data from the patient, or through report or assessment by family members or healthcare providers (Brown & Bussell, 2011; Byerly et al., 2007; Rand & Wise, 1994). Speicifically, subjective measures often involve healthcare provider's or patient's evaluation of their medication-taking behavior (Vik et al. 2004). And this can be done with interviewing patients by healthcare providers. For example, healthcare provider will ask patient about their medication knowledge including dosing schedules, any problems with taking medications to check the patient's adherenrce. Unfortunately, these subjective assessments by interviewers can increase bias adherence and this method is rare method to assess adherence (Vik et al. 2004). Another common subjective measure is patient's self-report. For this assessment, some providers may use direct questioning method which is similiar to interview method but it is less intensive procedure compared to interviewing method. For example, patients will either admit or deny about their nonadherence directly in this assessment. However, this method may increase bias since some patients who claim adherence to avoid disapproval of others (Vik et al. 2004). Especiallly, patietns who tend to underreport medication-NA more likely to escape the embarrassed moments from their healthcare provider (Vik et al., 2004).

Objective Measures. Objective measures provide more precise records than subjective measures since objective measures are quantitative (Anghel et al., 2019). Objective measures can be divided into (a) direct measures, and (b) indirect measures such as electronic medication monitoring, biochemical measurements from drug levels on blood (Hill, 2005; Krcmarik, 2018; Liu et al., 2001; Partridge et al., 2002). Direct measure is a measurement that is directly verifying medication administrations, including direct observation by healthcare professionals and measurements of the drug concentration. Direct objective methods are mostly used for research studies with single-dose therapy or intermittent administration during hospitalized period (Vermeire et al., 2001). Indirect methods are more popular than direct methods in medication adherence research due to better financial benefits and time constraints, including pill count, electronic monitoring recording devices, and secondary database analysis measures (Anghel et al., 2019).

- **Pill Count.** Pill counts add up the number of dosage units that a patient has taken between two visits. This number would then be subtracted from the total number of units received to find the adherence information (Anghel et al., 2019; Farmer, 1999). This method is simple and cheaper to conduct research. However, several limitations are identified, such as (a) difficulty in assessing non-discrete dosages in medication formulation (fractionated tablets, capsules, and actuated inhaler); and (b) missing doses due to using medication only as needed (Pro Re Nata or PRN) (Vik et al., 2004).
- **Electronic Monitoring Devices.** Electronic monitoring devices are tools formed in prescription medication packages to record dosing events and store records of

adherence (Checchi et al., 2014). Medication Event Monitoring System (MEMS) is one of the popular electronic monitoring devices that has a sensor in the medication package container (e.g., once the package opens, it will send the signal to record as medication is taken). This device assumes that opening the container is ingesting medication (Lam & Fresco, 2015). Many studies support the accuracy of the MEMS device, and often it is considered as a reference standard for validating other adherence tools (Diaz et al., 2001; Lam & Fresco, 2015; Modi et al., 2012; Vitolins et al., 2000; Vik et al., 2004). However, there are several issues about MEMS such as (a) high costs, (b) difficult application for other types of medication formulations (e.g., liquid forms cannot be dispensed easily with MEMS), and (c) incorrect use of the MEMS (i.e., opening the medication container without taking the medication) (Diaz et al., 2001; Lam & Fresco, 2015; Modi et al., 2012).

- **Measures Involving Secondary Database Analysis.** The data of the secondary database can be captured in primary data systems, such as electronic prescription services or pharmacy insurance claims (Lam & Fresco, 2015). Centralized-computerized systems are critical to review prescription refill records along with prescribers' and dispensers' information over that designated period (Farmer, 1999). This system allows an analysis of big datasets and assesses multi-drug adherence easily (Kitahata et al., 2004). Although, it could be hard to identify some medication adherence factors (i.e., patient's self-efficacy) since this data is not available in electronic health records (Krousel-Wood et al., 2013). There are

three major ways to assess medication adherence, which are medication possession ratio; proportion of days covered; and new prescription medication gap.

(a) Medication Possession Ratio. Medication possession ratio (MPR) is defined as the proportion (or percentage) of days medication was supplied during a specified time period (i.e., last refill is the end point, or fixed refill) (Andrade et al. 2006; Burnier & Vrijens, 2018). The MPR is easy, and it is a widely used method. In contrast, the major drawback of MPR is that it does not consider the gaps in refills (Burnier & Vrijens, 2018; Lam & Fresco, 2015; Vanderpoel et al., 2004). Moreover, MPR only has the time of prescription collection and no exact medication administration information (i.e., missed a dose or stopped, patient may refill early for vacation), so it can affect overestimated adherence (Lam & Fresco, 2015).

(b) Proportion of Days Covered. Proportion of days covered (PDC) estimates the number of days covered over a time interval (Burnier & Vrijens, 2018). In 2012, the PDC is becoming the preferred adherence measurement and recommended by the Pharmacy Quality Alliance (PQA) as the standard measure (Nau, 2012; Prieto-Merino et al., 2021). If a patient refills the medication several days prior to running out of it, PDC makes an adjustment, whereas MPR will be elevated from overlapping days supplies (Burnier & Vrijens, 2018). The PDC can provide a more conservative estimate of the adherence information even patient has switches of medications (Martin et al.,

2009). Both PDC and MPR cannot measure if a patient skipped taking medications several days before refiling it (Burnier & Vrijens, 2018; Prieto-Merino et al., 2021). Persistence in PDC can be defined as continuous use of the therapy over a fixed time interval before discontinuation (Patel et al., 2020). However, it can be tricky to assess and measure the discontinuation time frame. Generally, researchers set the date of gap between two consecutive prescription refills (i.e., 45 or 60 days) over the entire observation. For example, Patel et al. (2020) assessed discontinuation time frame when patient's refill gap is bigger than 45 days.

(c) New Prescription Medication Gap. New Prescription Medication Gap (NPMG) is defined as the proportion of days within an interval bounded by the prescriber's initial record date (prescriber's prescription order date) and the end of the observation period (Karter et al., 2009). The gap will be determined by researcher depending on the medications. This measure starts with the date of prescription and includes the time until initiation than MPR or PDC (Burnier & Vrijens, 2018). The NPMG ranges from 100% for patients who obtain no medication to 0% for those who consistently refill their medication in a timely fashion (Burnier & Vrijens, 2018). However, this measure does not calculate nonadherence values for cumulative periods without considering the possibility of early refill or overfill (Burnier & Vrijens, 2018).

Oral Endocrine Therapy (OET). OET includes either tamoxifen or aromatase inhibitors (AIs), which are anastrozole, exemestane, and letrozole (Lundgren et al., 2018). Theses AIs are recommended treatment in early stage breast cancer in postmenopausal women. This medication are given to patients after their surgery, chemotherapy or radiation, to lower the risk of the cancer recurrence (Xu et al., 2019).

OET Medication Dosage. The typical dose of Exemestane (25 mg Daily), Letrozole (2.5 mg daily), or Anastrozole (1 mg daily) in Postmenopausal Women (Peters & Tadi, 2022).

OET Medication Day's Supply. The quantity of dispencing amunt of each refill is typically 30 days and 90 days (Taitel et al., 2012).

OET-NA. Patients are not taking prescribed OET with PDC of < 80%; patients are not taking for various reasons such as (a) the patient's own decision, and/or (b) simply not taking as prescribed (Haynes, 1976).

Older Adults. Older adults or geriatric populations are commonly viewed as anyone over 65 years-old (Butler et al., 2011; Sieber, 2007).

Over-adherence. Ruddy et al. (2009) presented a definition of over-adherence as taking too much of a medication.

Description of the Problem

For this section, I will introduce the impacts of chronic disease, cancer, breast cancer, and population of older breast cancer patients in the United States. Also, I will present health behavior, and its terminology to understand complex issues such as medication-NA. The final section is focused on medication-NA behavior in older breast cancer patients that

intersect all previous descriptions of the problem. This information will be the foreground of my RESILIENT study.

Chronic Disease

The Centers for Disease Control and Prevention (CDC) (2003) defined chronic disease as a wide range of conditions that have a long-lasting character (i.e., lasts 1 year or more), a lack of spontaneous cure, and no possibility of being completely cured. Examples include: heart disease, cancer, chronic lung disease, stroke, Alzheimer's disease, diabetes, and chronic kidney disease. Multiple agencies and scholarly articles defined chronic disease as having characteristics such as duration or latency, need for medical attention, effect on function, pathology, departure from well-being, noncontagious nature, multiple risk factors, and nonamenability to cures (Bernell & Howard, 2016; CDC, 2022; Goodman et al., 2013; Paleczna, 2018; Phillips & Currow, 2010; WHO, 2014). In 2016, the total cost of treating chronic diseases within the United States was $1.1 trillion, approximately 20% of the United States' gross domestic product (Waters & Graf, 2018). This trend has continued, as chronic diseases (i.e., heart disease, diabetes, and cancer) were the leading drivers of annual health care costs at $3.8 trillion in the US in 2021 (CDC, 2022). Supporting patient self-care is the most critical component for effective chronic disease care which can lead to improved health outcomes (Bennett, 2016; Coleman & Newton, 2005; Dickson et al., 2013; Evangelista & Shinnick, 2008). Self-care can be defined as providing adequate attention to an individual's own health-related physical and psychological well-being (Beauchamp & Childress, 2001). Self-care is derived from the patient's understanding of disease progression management and symptom control (Donovan, 1995; Thorne et al., 2003; Wagner et al., 2001). Patients with chronic diseases are required to make everyday health-related self-care decisions (Thorne et

al., 2003). This is due to the majority of treatments being heavily related to a patient's self-care, such as taking medications and following up with healthcare providers (Evangelista & Shinnick, 2008). Buttorff et al. (2017) reported that 60% of American adults had at least one chronic disease, and 12% of them had more than five chronic diseases. The average annual healthcare cost of public insurance (i.e., Medicaid, Medicare, any insurance by U.S. federal, state, or local governments) is $19,201 for a patient with more than five chronic diseases (Buttorff et al., 2017).

Unfortunately, with 81% of the population diagnosed at least one chronic disease, patients 65 years and older are the age group that collectively suffers the most from chronic diseases (Buttorff et al., 2017). The National Council on Aging (NCOA) (2021) reported the top 10 most common chronic diseases in older adults are hypertension, hyperlipidemia, arthritis, ischemic/coronary heart disease, diabetes, chronic kidney disease, heart failure, depression, Alzheimer's disease and dementia, and chronic obstructive pulmonary disease (COPD). Moreover, there is concern with an increasing number of individuals with chronic diseases (Hagger & Weed, 2019; Ryan, 2009). The CDC demonstrated that aging increases the risk of chronic disease. In 2019, 16% of Americans were older than 65, and by 2060 25% of the population will be older than 65 (CDC, 2022). The importance of understanding chronic diseases will continue to expand as the older adult population increases. Individuals with chronic diseases tend to have more limitations in terms of cognitive impairments (i.e., blindness, hearing loss, memory loss), and functional impairments (i.e., urinary incontinence, physical weakness, and use of a walker or cane) (Buttorff et al., 2017; Hung et al., 2011). These limitations can pose greater threats to their health outcomes than other age groups

(Buttorff et al., 2017) by impacting their ability to adhere to self-care behaviors (Evangelista & Shinnick, 2008; Hung et al., 2011).

Cancer

The lifetime risk of having a cancer diagnosis is about 40% in the general population (White et al., 2014). Today, more patients are living with cancer for longer periods of time since their survival increases with medical treatments. The American Cancer Society (ACS) defines cancer as a chronic disease when it becomes stable and controllable with treatments or reaches remission (ACS, 2019). Possible treatments include surgery, chemotherapy, and/or radiation. All oral anti-cancer medications are considered chemotherapy. There has been remarkable growth and development of oral anti-cancer medication in the last decade, and more than 30% of anti-cancer medications are now available as oral agents (Weingart et al., 2011). More cancer patients prefer to have oral anti-cancer medications compared to intravenous therapy (IV) (Verbrugghe et al., 2013; Wood, 2012). However, with the possibility of oral anti-cancer medication there is also the chance of medication non-adherence (NA). Non-adherent patients suffer cancer relapse 2.5 times more often than adherent patients (Wood, 2012). However, it is not easy to measure NA since many patients take oral anti-cancer medication in a home setting (Given & Given, 2016).

Over the last two decades, oral anti-cancer medications have become a primary form of cancer treatment (Greer et al., 2016). The field of oral anti-cancer medication adherence research has grown steadily to include various types of cancer in different populations (Borner et al., 2001, Bouwman et al., 2017; Hansen, 2012; Verbrugghe et al, 2013). Oral anti-cancer medication treatments not only improve survival rates but also enhance the

quality-of-life for cancer patients. However, cancer patients face challenges regarding oral anti-cancer medication-NA (Weingart et al., 2007).

Breast Cancer. Breast cancer is the most commonly diagnosed cancer, which is make up 11.6% of total cases, along with lung cancer, for the female population, and the leading cause of cancer deaths even with prescribed therapy (Bray et al., 2018). Only between 41% and 72% of breast cancer patients fully adhered to oral anti-cancer medications, especially for the endocrine-related oral anti-cancer medication (Hurtado-de-Mendoza et al., 2018).

Older Women with Breast Cancer. The risk for most cancer, including breast cancers, increase with age (Alkabban & Ferguson, 2021). Altekruse (2009) demonstrated that the incidence of breast cancer increases dramatically with age, and the mortality is higher for older women (>65 years). Zhu et al. (2020) also found a positive association between accelerated aging in breast cancer survivors and mortality. Older women face various challenges in maintaining adherence due to physical function, side-effects, drug to drug interactions, cognitive effects, psychological status, altered nutrition status, lacking knowledge of medication regimens, and financial issues (Given & Given, 2016). According to the Surveillance Epidemiology and End Results (SEER) registry and Breast Cancer Research Foundation (BCRF), the median age of a breast cancer diagnosis was 62, and more than 20 % of newly diagnosed women were older than 70 years in 2021. As the general population ages, breast cancer cases will double by 2030 in the United States, and women over 70 years old will be a significant population with breast cancer (BCRF, 2021).

The pathophysiology of breast cancer in the older adults is the same as in younger populations, and nearly 80% of cases are an estrogen-positive (ER+) type (BCRF, 2021). Luminal cells, which are the epithelial cells of mammary, can be part of the production of estrogen and progesterone receptors (Yersal & Barutca, 2014). Older women with ER+ breast cancer have more favorable subtypes such as luminal A (low histological grade, low degree of nuclear pleomorphism, low mitotic activity and include special histological type with good prognosis), but they are mostly less aggressive (Jenkins et al., 2014; Yersal & Barutca, 2014). This suggests that oral endocrine therapy (OET) will be more effective treatment for older as well as younger populations. The OET is standard therapy for ER+ breast cancer and works by blocking hormone receptors that fuel cancer growth (ACS, 2015; Milata et al., 2018). Unfortunately, 70% of breast cancer patients prematurely stop taking it before the end of the recommended 5-year period (Luschin & Habersack, 2014). More recently, trials suggest that OET should be administered for 10 years rather than 5 years (Milata et al., 2018). This new recommendation causes even more concern about OET-NA since it doubles the medication taking time and increases the difficulty of monitoring patients' self-administration of the medications.

Older Adults with Medication-NA. About 90% of older adults take at least one prescription medication, and 54% of them take four or more medications (Kirzinger et al., 2019). Medication-NA occurs in around 50% of older adults, and its adverse consequences include worsening health, increased risk of mortality, and greater health care costs (Gosmanova et al., 2015; Iuga & McGuire, 2014; Lee et al., 2018; Marcum et al., 2017; Sokol et al., 2005). Medication-NA results in substantial healthcare service costs in the US at

between $100 billion and $300 billion annually (Marcum et al., 2017). Unfortunately, medication-NA is a persistent issue among older adults, even though they have greater risk than younger adults (Lee et al., 2018). Older adults have unique issues that influence medication-NA at the drug, patient, provider, and healthcare system levels, including: (a) increased vulnerability to drug-related problems because of age-related changes in pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion) and pharmacodynamics (the physiologic effects of the drug); (b) high prevalence of cognitive and functional impairments; and (c) increased cost burden of healthcare service use across settings and regimen complexity (Buttorff et al., 2017; Evangelista & Shinnick, 2008; Hung et al., 2011; Rochon et al., 2022; Smaje et al., 2018).

Unfortunately, many older breast cancer patients also suffer from medication-NA, which is one of the most complicated health behaviors. There are limited studies available to understand why older breast cancer patients are not regularly taking the OET medications, even though they have a greater risk of undertreatment linked to poor outcomes and increased mortality (Nardin et al., 2020).

Significance of the Problem

Medication-NA is not a new problem, and it dates back to Hippocrates, circa 500 B.C. (Osterberg & Blaschke, 2005). The World Health Organization (WHO) emphasized the issue of NA in 2003 when they published an adherence report of long-term therapies including cancer treatments (Sabaté, 2003). Approximately 80% of all breast cancer patients are prescribed OET at least five years, which increases survival rates, improves quality-of-life (QOL), and decreases recurrence rate, mortality, morbidity, and medical costs for women

with breast cancer (Brett et al., 2018; Harrow et al., 2014; McCowan et al., 2008; Murphy et al., 2012; Paranjpe et al., 2019). Adherence rates for OET vary widely, from 41% to 72%, though the studies have included small sample sizes (Hurtado-de-Mendoza et al., 2018). This indicates that we need to utilize larger samples to validate the rate of OET adherence. Moreover, there are varied rates of medication-NA in breast cancer. Breast cancer patients over 69 years old had a higher medication-NA, which has not been documented in patients with other kinds of cancer (Gieseler et al., 2019; Verbrugghe et al., 2013). Therefore, it is critical to investigate the multi-level determinants that contribute to OET-NA in older women with breast cancer.

Incidence and Prevalence

More than 1.7 million people are diagnosed and treated for breast cancer each year worldwide (Golubnitschaja et al., 2016; Torre et al., 2015). In the United States, breast cancer is the most prevalent cancer in females and is the second-highest cause of all cancer deaths with 268,600 new cases and 41,760 deaths in 2019, even with prescribed therapy (Park et al., 2019; Siege et al., 2019). OET is the most prescribed medication therapy for breast cancer (Wen et al., 2017).

Outcomes

As survival rate depends on patient adherence to treatment, it is critical to understand adherence to OET. Currently, OET-NA rates range from 41% to 72% measured by various methods (i.e., self-reports, indirect observations from electronic medication monitoring, and biochemical measurements) (Hurtado-de-Mendoza et al., 2018). Hwang et al. (2020) reported that 70% of breast cancer patients discontinue their recommend OET regimen before 5 years. Non-adherent women with breast cancer face diminished QOL and increased recurrence rates

and mortality. The risk of breast cancer recurrence is 1.44 times higher for OET non-adherent patients than adherent patients (Sanft et al., 2019). Low adherence to OET is related to a 30% increased risk of mortality due to cancer recurrence (Brett et al., 2018; Harrow et al., 2014; Murphy et al., 2012).

Cost

Increased medical costs have become a bigger problem in the breast cancer population as the number of older breast cancer patients continues to increase in the U.S. Due to the high percentage of breast cancer patients on Medicare, this has led to a greater cost burden on the US government, with projected costs of $20.5 billion on breast cancer care alone in 2020 (Xie et al., 2020). Older adults with breast cancer are already considered a high-risk population due to their increased vulnerability to drug-related problems because of age-related changes in (a) pharmacokinetics and pharmacodynamics (the physiologic effects of a drug); (b) high prevalence of cognitive, and functional impairment; and (c) increased cost burden of service use across settings and regimen complexity (Buttorff et al., 2017; Evangelista & Shinnick, 2008; Hung et al., 2011; Rochon et al., 2022; Smaje et al., 2018). These age-related changes contribute to increasing cost of care which then lead to OET-NA and overall strain on the healthcare system (Brett et al., 2018; Harrow et al., 2014; McCowan et al., 2008; Murphy et al., 2012; Paranjpe et al., 2019).

Conceptual/Theoretical Framework

Ecological Systems Theory

Berben et al. (2012) recommended that healthcare researchers utilize a multilevel ecological perspective for medication adherence such as Bronfenbrenner's ecological system theory (EST). This is because medication adherence issues may be not only influenced by

multiple factors—including a patient's social environment of family, friends, community—but also because the multiple factors can wield influence simultaneously and reciprocally (Berben et al., 2012).

Purpose, Scope, and Origin of Ecological System Theory

The EST was first developed for evaluating and understanding the development of children; however, the multilevel approach works well for understanding etiological impacts on health and behavior in adults and has been widely used for that purpose (Bronfenbrenner, 1977). The EST proposes that human development happens in a complex process within the individual and the environmental contexts of which he or she is a part (Bronfenbrenner, 1977). The scope of ecological system theory is very broad and has primarily been used in psychology, however, it has also been applied in other disciplines such as nursing, sociology, pharmacology, and medicine. Initially, the EST was designed to explain environmental factors that contribute to childhood development (Bronfenbrenner, 1977). Likely due to its multi-system emphasis, the EST has frequently been applied to healthcare interventions and used to improve health outcomes (Golden & Earp, 2012).

Bronfenbrenner's theory is a grounded theory from human development science (Bronfenbrenner, 1977). Bronfenbrenner's theory was well known as a socio-ecological model before he published the first version of his theory in 1977 (Rosa, 2013). Bronfenbrenner added the individual level to his theory in 1983 (Bronfenbrenner, 1983). After 1993, Bronfenbrenner changed the name of his theory to bioecological theory in order to focus on the component of human developments (Rosa & Tudge, 2013). Bronfenbrenner started to call his theory "ecological system theory" after 2000 (Bronfenbrenner, 2000).

Content of Ecological System Theory

Assumptions. The ecological system theory (EST) assumes that there are interrelations between individuals and their environment (Bronfenbrenner, 1977; Golden & Earp, 2012). The multiple levels of environmental effects interact and reinforce patients' behaviors to improve health conditions (Golden & Earp, 2012). Bronfenbrenner (1977; 1979) assumed that there is a reciprocal relationship between levels and fluctuations in the social environment and individual behavior.

Concepts. Bronfenbrenner (1977; 1983;1994) identified variables for system-thinking at multiple levels: individual-, micro-, meso-, exo-, macro-, chrono-system levels. The micro-system shows interpersonal relationships in an environmental background (Bronfenbrenner, 1977; Yach, 2002). The micro-system involves direct interpersonal relationships, like a patient's family and peer group (Bronfenbrenner, 1977). The meso-system addresses the connection between environmental settings (Bronfenbrenner, 1977; Yach, 2002). The meso-system describes the interaction between micro-systems that contribute to healthy behaviors like medication adherence (Bronfenbrenner, 1977). The exo-system describes the indirect environmental settings that exert influence without active patient engagement (Bronfenbrenner, 1977). The macro-system refers to broader systems that include culture or subculture, such as the economic, social, education, healthcare, legal, and political systems (Bronfenbrenner, 1977; McLeroy et al., 1988). Lastly, the chrono-system applies to the changes over time that affect an individual's development and includes life transitions such as marriage, divorces, school entry, and relocation (Bronfenbrenner, 1994). Bronfenbrenner added the individual level of concept in 1983. The individual level is considered to be a patient-system that includes demographics, knowledge, self-efficacy, and

medication beliefs (Bronfenbrenner, 1983; Yach, 2002). Based on its multi-system emphasis, Bronfenbrenner's EST has been frequently utilized in public health interventions and promotions to improve health outcomes (Golden & Earp, 2012).

Theory Application: EST

Bronfenbrenner's ecological systems theory (EST) was used to assess the effect of multi-level factors on medication adherence (Berben et al., 2012). The multilevel nature of EST is a foundational premise of my research. In my dissertation, I assert that individual-, micro-, meso-, exo-, and macro-level systems modulate breast cancer oral endocrine therapy (OET adherence). For example, a patient's (a) psychosocial concerns (individual-system); (b) interpersonal relationship with chemotherapy clinic workers (micro-system); (c) significant other involved in routine care (meso-system); (d) consumption of mass media, involvement in the cancer community, and utilization of social services (exo-system); and (e) cultural background (macro-system) may influence treatment adherence.

Importance to Nursing

The ecological system theory reflects the nursing metaparadigm, including concepts of person, nursing, environment, and health (Masters, 2018). Even though EST is a psychology theory, each concept connects well to nursing within nursing metaparadigms. From the nursing metaparadigm, the concepts of person correspond with patient/individual level in the ecological system theory, the concepts of nursing can be comparable to ecological experiments in the EST, and the concepts of health are equivalent to human development in the EST. Since the goal of human development is to improve quality of life. The ecological system theory has been utilized in the nursing field to enhance a patient's

behavior with structured theoretical backgrounds (Berben et al., 2012, Cannoy et al., 2019; Denhaerynck et al., 2017; Hall et al., 2016).

The Five-Dimension Model (FDM) of the World Health Organization (WHO)

The five-dimension model (FDM) for medication adherence was developed by the World Health Organization (WHO) (Sabaté, 2003). The FDM considers patient-related, socio-economic, therapy-related, condition-related, and health care team/system-related factors (Sabaté, 2003). In the WHO's five-dimension model, (a) patient-related factors include a patient's knowledge, attitude, self-efficacy, beliefs on treatment efficacy, and perceived barriers to adherence; (b) social and economic-related factors include social networks, family functioning, and the cost of medication; (c) therapy-related factors include side-effects of the regimen, duration of treatment, and dose complexity; (d) condition-related factors involve co-morbidities, depression, and other psychiatric diagnoses such as substance abuse; and (e) healthcare team/system-related factors consider the knowledge of healthcare professionals and the relationship between the patient and their healthcare team (Sabaté, 2003).

Theory Application: FDM

Berben et al. (2015) demonstrated that the FDM and EST to enhance medication adherence by addressing (a) patient-level (i.e., patient beliefs, intentions, self-efficacy and barriers, confidence in immunosuppressive medication, depression, health literacy); (b) healthcare provider-level (i.e. patient satisfaction with the interpersonal dimension of care, trust in the transplant team, social support); (c) healthcare organization-level (i.e. chronic illness management, transplant program practice patterns); and (d) healthcare system and

policy-level (i.e. perceived financial burden of the treatment regimen, insurance status, system of healthcare coverage, country) factors.

Since the FDM and Bronfenbrenner's EST utilize ecological concepts to understand medication adherence, I would like to apply these theoretical models to the issue of medication non-adherence in women with breast cancer. Combining Bronfenbrenner's EST with the WHO's FDM can account for the simultaneous, reciprocal interactions between multi-level factors. For example, the EST's individual-level correlates to the FDM's patient-related factors. Both categories discuss patient attitudes, knowledge, and self-efficacy (McLeroy, et al., 1988). The EST's micro-level encompasses the FDM's social and healthcare team-related factors which describe interpersonal or face-to-face relationships with healthcare providers, as well as social support. The EST's meso-level correlates with the FDM's healthcare team-related factors including the characteristics of the healthcare organization where a patient is being treated. The EST's macro-level factors relate to the FDM's healthcare system-related factors including local, state, and national healthcare-associated laws and policies.

Importance to Nursing

Investigating FDM factors will help nurses understand the current issues of OET-NA clearly. The blueprint of FDM factors can guide nurses to educate their patients on the importance of medication adherence to treat breast cancer. Nurses can coach patients at each of the levels (patient-related, condition-related, therapy-related, social/economic-related, and health care team/system-related factors) to influence their behavior changes. By promoting

OET adherence behavior, more breast cancer patients can eventually enhance their QOL and decrease recurrence rate, mortality, and medical costs.

Innovation

This study is novel because of its use of large database to increase the sample size and its investigation of multi-level determinants of OET-NA. Existing studies have commonly overlooked multi-level determinants, recruited homogenous samples, and utilized small samples from the Electronic Health Record (EHR), both of which limit generalizability. To overcome these issues, this study will utilize secondary data analysis with a large database, which is a Health Insurance Portability and Accountability Act (HIPAA)-compliant EHR patient database of over 158 million patients in 863 healthcare facilities across the United States (Bao et al., 2018; Jamil et al., 2019). Additionally, this study will be the first to investigate potential underlying multi-level influences on OET-NA for breast cancer patients. This study will apply Bronfenbrenner's EST and FDM to better understand potential multi-level influences in order to improve OET-NA, which has the potential to decrease morbidity/mortality and increase QOL for breast cancer patients.

Conclusion

Chapter one defined medication non-adherence related terminologies. I also described the current issues that women with breast cancer face, as well as the benefit of using Bronfenbrenner's EST and FDM. Medication-NA is a complex problem that causes poor health outcomes and increased healthcare costs. The EST is an appropriate framework that can be related to FDM to enhance understanding of OET-NA. Identifying the role of multi-level determinants like patient-related, socio-economic-related, therapy-related, condition-related, and healthcare team/system-related factors will provide a blueprint for future tailored

interventions specific to breast cancer patients on OET. In this study, I will focus on identifying the rate of OET-NA and the multi-level determinants related to OET-NA in women with breast cancer in order to improve adherence to OET. This will serve to eventually enhance QOL and decrease recurrence rates, mortality, and medical costs for women with breast cancer.

CHAPTER 2

LITERATURE REVIEW

This chapter aims to present the state of the science in OET-NA among older women with breast cancer from existing studies and identifying the gaps in the literature. The findings of this chapter can justify the RESLIENT study's research questions and methodologies.

Breast Cancer

Incidence and Prevalence

Breast cancer is the most common cancer diagnosed in women, and it is the second most common cause of death from cancer among women in the world (Alkabban & Ferguson, 2021). The average risk of an American woman developing breast cancer sometime in her life is about 13%, and there are more than 3.8 million breast cancer survivors in the United States (ACS, 2022a; Parada et al., 2019; Gucalp et al., 2019). Annually 300,000 new breast cancer cases are reported in the United States, and 40,000 American women die from breast cancer each year (Park et al., 2019; Siege et al., 2019). There is a positive association between age and the incidence rate of breast cancer. For example, women 20 to 24 years of age have 1.5 cases per 100,000 women, and women 75 to 79 years of age have 421.3 cases per 100,000 women annually in the United States (Alkabban & Ferguson, 2021). According to the American Cancer Society the median age of breast cancer diagnosis among American women is 62 years. Breast cancer rates among American women in various racial and ethnic groups are: non-Hispanic white (128.1 cases), African American (124.3 cases), Hispanic/Latina (91.0 cases), American Indian/Alaska

Native (91.9 cases), and Asian American/Pacific Islander (88.3 cases) per 100,000 annually (ACS, 2022a).

Pathophysiology

In the anatomical presentation, the breast lies on the pectoralis major muscle and supportive ligaments on the chest wall (Alkabban & Ferguson, 2021). According to National Cancer Institute (NCI), the breast has milk-producing glands, no muscle tissue, and a layer of fat surrounding the glands. The glandular tissues include the breast lobes and breast ducts. Each breast contains 15 to 20 lobes circularly, and each lobe is formed by lobules containing milk production glands in response to hormone stimulation. Ducts are the roads that connect the lobes, lobules, and glands.

There are blood and lymph vessels throughout each breast. Lymphatic vessels are connected to axillary nodes and drain lymph fluids in breast tissue. Lymph fluids contain white blood cells known as lymphocytes that are immune cells (Memorial Sloan Kettering Cancer Center, 2022). Breast cancer develops from DNA damage and genetic mutations that can be enhanced by estrogen or progesterone hormones. Cancer cells keep growing, tricking the immune system to stay alive, ignoring other cell signals, and spreading into nearby areas via lymph vessels or another route (NCI, 2021). Researchers found that there are predisposed populations who have DNA defects with pro-cancerous genes like BRCA1 and BRCA2 (Alkabban & Ferguson, 2021). Breast cancers spread and are found frequently in lymph nodes such as axillary lymphatic plexus, cubital lymph nodes, superficial axillary (low axillary), deep axillary lymph nodes, brachial axillary lymph nodes, interpectoral axillary lymph nodes (Rotter nodes), para-mammary or intramammary lymph nodes, and para-sternal lymph nodes (internal mammary nodes) (NCI, 2021).

Physical Presentation

Unfortunately, there is no clear visual presentation in the early stage of breast cancer and most early breast cancer patients are asymptomatic. However, once the size of breast cancer increases, the patient may discover cancer as a lump, which can be swollen lymph nodes, during showering. If the breast cancer grows more prominent, the patient may present peau d'orange, which is a French term meaning orange skin, to describe a symptom in which cancer cells make the skin thick and red by blocking lymphatic systems (Alkabban & Ferguson, 2021).

Staging Breast Cancer

Breast cancer staging is selected through physical examination, imaging studies, and pathologic examination of the tumor and involved lymph nodes after surgical treatment. Staging is essential for categorizing risk factors that determine prognosis and guiding treatment recommendations for breast cancer patients (ACS, 2021; Alkabban & Ferguson, 2021).

The earliest stage of breast cancer is Stage 0, which is carcinoma in situ, has abnormal cells that are present but have not spread to nearby tissues (Trayes,& Cokenakes, 2021). After that, stages range from Stage I (1) through IV (4), and a lower number means a lower stage and less spread of cancer. Moreover, healthcare providers commonly use additional tools to differentiate stages of cancer including: the Tumor (T), node (N), and metastasis (M) (TNM) classification system, Estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor (HER) 2 status, and the grade of the cancer (G) (ACS, 2021; Alkabban & Ferguson, 2021).

The TNM classification system was made by the American Joint Committee on Cancer (AJCC) and has both clinical and pathologic staging systems for breast cancer (ACS, 2021). The TNM classifications include the primary tumor size (T), the number of involved lymph nodes (N), and any distant metastasis (M) (ACS, 2021; Alkabban & Ferguson, 2021). The ER and PR status show if the cancer has estrogen or progesterone receptors. The HER2 status demonstrates if the cancer makes too much of a protein called HER2, which is the mediator of key pathways involved in invasive behavior and cancer cell growth. The grade of the cancer (G) predicts the patient's outcome or prognosis and helps treatment recommendations. Possible grades span from 1 to 3, and a lower grade means slower growth and that the cancer is less likely to spread.

Treatment

Treatments are recommended to reduce the chance of local recurrence and the risk of spreading cancer (metastasis). Surgery is the main treatment of breast cancer with or without radiotherapy. Medical oncology therapy is recommended when there is a risk of metastatic cancer (Rocque et al., 2018; Seroussi et al., 2018).

Surgical Oncology

Surgery is the primary intervention to control breast cancer. Radical Mastectomy of Halsted (RMH) had been utilized— which removed the breast, axillary lymph node, and pectoralis muscles— but it is no longer recommended due to high morbidity and mortality rates. Currently, the Modified Radical Mastectomy of Patey (MRMP) is the more favorable method to remove the whole breast tissue with the axillary lymph nodes. When a patient has a small tumor with negative sentinel lymph nodes, breast-only removal without axillary dissection can be recommended as a simple mastectomy. Breast-conserving surgery (BCS)

removes the tumor with leaving as much normal breast as possible; it is also called lumpectomy, quadrantectomy, partial mastectomy, or segmental mastectomy depending on how much breast tissues are removed together (ACS, 2021; Alkabban & Ferguson, 2021).

Radiation Oncology

Radiation therapy can decrease the risk of cancer recurrence by 50% at 10 years and cancer death by 20% at 15 years of follow up after BCS. Radiation therapy is more beneficial in large-sized tumors (> 5 cm), or other organ-involved tumors (e.g., skin, chest wall and lymph nodes). Two main types of radiation therapy are available: external beam radiation (teletherapy) and internal radiation therapy (brachytherapy). External beam radiation (EBR) therapy is radiation directly delivered at the patient's cancer site. The EBR approach uses different levels of radiation depending upon tumor location. For example, low-energy radiation would not penetrate deeply into the body. Gamma Knife is one of the EBR techniques, and it is a highly advanced and precise method that uses a concentrated radiation dose from Cobalt-60 sources. Another type of radiation is brachytherapy, which involves placing radiation sources near the tumor site. Those radiation sources can be rods or small objects, and they can be inserted directly into the tumor-site. These may be left in place several days or permanently to reduce cancer cells (SEER, 2022a).

Radiation may be not necessary when a patient is over 70 years of age or older and they have small tumors without lymph node related spread even with hormone sensitive (ER+ or PR+) breast cancer. This is due to limited studies supporting radiation leading to an increased survival rate in these cases. Specifically, the prognosis was unfavorable regarding the need to continue hormonal therapy taking of OET for at least 5 years. Radiation can also be utilized as palliative therapy in advanced cancer stages— for example, when the tumor

has spread to the central nervous system (CNS) or bone— to shrink cancer cells or slow down their growth. This can relieve pressure or a blockage to reduce pain (Tang et al., 2018; Wang et al., 2018).

Medical Oncology

Adjuvant chemotherapy is a therapy that patients receive after their primary treatment, such as surgery or radiation. This therapy is a systemic treatment which includes cancer medications (chemotherapy) such as cytotoxic therapy, immunotherapy and hormone therapy in medical oncology. In the last two decades, anti-cancer medication paradigms have evolved from non-specific cytotoxic agents to mechanism-based therapeutics (Vanneman & Dranoff, 2012). Initially, many anti-cancer drugs were focused on killing rapidly dividing cells, and this is still a backbone of current treatment. However, recently, more treatment options have been included such as targeted therapy combined with immunotherapy (Vanneman & Dranoff, 2012). Targeted therapy stops molecular pathways that are critical to tumor growth and maintenance, whereas immunotherapy stimulates the immune systems to fight tumors (NCI, 2019; Vanneman & Dranoff, 2012). Only 17% of breast cancer patients need targeted therapy to reduce the growth-promoting protein HER2. Frequently, Trastuzumab is recommended, and it reduces the risk of recurrence by 19% (Alkabban & Ferguson, 2021).

The cytotoxic drugs can reduce relapse 25% over a 10 to 15-year period by using a first-generation cytotoxic chemotherapy regimen such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) every six months. In addition, other types of cytotoxic drugs are available such as Anthracyclines (doxorubicin or epirubicin) and taxanes, the most

commonly used cytotoxic agents for early and advanced stage breast cancer for a three-to-six-month period.

Hormone therapy medication blocks the growth of breast cancer that use hormones as a fuel to grow. Hormone therapy was superior to other types of chemotherapy in increasing breast cancer patients' quality-of-life (Burstein et al., 2019). The OET is a standard therapy for estrogen receptor-positive breast cancer including tamoxifen, and Aromatase Inhibitors (AIs) as anastrozole, exemestane, and letrozole (ACS, 2015; Milata et al., 2018). Commonly, tamoxifen (TAM) is a recommended drug for premenopausal women, and AIs are common drugs for postmenopausal women. According to Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2015), TAM and AIs reduce the risk of recurrence by about 30% with TAM, and around 40% with AIs during the first 10–15 years respectively. In spite of the benefit of taking OET for five years, early-stage ER+ breast cancer still has a higher risk of late recurrence and death (Pan et al., 2017). There are several studies that show a benefit of extending OET with TAM for 10 years versus stopping treatment at 5 years (Davies et al., 2013; Goss et al., 2016). Their results demonstrated that extended TAM treatment lowered recurrence by 3.7 %, extended AI treatment reduced recurrence by a range of 3-4 %, and mortality also dropped by 2.8%. Still international guidelines have not included the extended (10 year) therapy regimen, but it is expected to change to taking OET for 10 years rather than 5 years (Eraso et al., 2021).

Oral anti-cancer medication-NA is known to decrease survival rates and quality-of-life (Borner et al., 2001). Anti-cancer medication-NA rates varied widely, from 46% to 100% for adult patients (older than 18 years old) (Bouwman et al., 2017; Greer et al., 2016;

Hansen, 2012). The field of oral anti-cancer medication-NA research has grown steadily to include various types of cancer in different populations, such as pediatric and adolescent patients (younger than 18 years old), adult (older than 18 years old), and older adult (older than 65 years old) (Borner et al., 2001, Bouwman et al., 2017; Hansen, 2012; Verbrugghe et al., 2013). The median age of cancer occurrence is around 65 years old, which indicates that older adults are the high-risk population (Howlader et al., 2016). However, many breast cancers patients are already suffering from OET-NA even with the shorter period therapy. Luschin and Habersack (2014) demonstrated that 70% of breast cancer patients prematurely stop taking it before the end of the recommended 5-year period. This new extension of treatment causes more concerns about OET-NA since we do not know the specific rate of OET-NA and the factors of affecting OET-NA within a theoretical framework such Bronfenbrenner's EST or WHO's FDM.

Medication Adherence in Chronic Diseases, Cancer, and Breast Cancer

Medication adherence is simultaneously influenced by multiple factors and frequently compromised by more than one barrier (Sabaté, 2003). This is because medication adherence is influenced not only by individual characteristics, but also by factors within the patient's environment, which are called system level factors. For this literature review, I have used a "funnel down" approach to identify and compare medication-NA factors between chronic disease and breast cancer. In order to investigate current literature trends of medication adherence in chronic disease, I performed a systematic literature search using the databases of Cumulative Index of Nursing and Allied Health (CINAHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Scopus, and Google Scholar. Selected articles in

this section have these criteria: (a) patients were older than 16 years and had chronic diseases; (b) patients took medications orally; (c) researchers used single quantitative studies and systematic reviews (contains only quantitative studies); (d) published before September 2022; and (e) written in English. Studies with qualitative designs were not included since these findings could skew the objectiveness of the data. I aimed to summarize the evidence for determinants that are widely applicable across different conditions, therapies, and regions/settings.

I utilized the concept of the WHO's FDM to organize medication-NA for my review. This model has been applied in numerous medication adherence studies to isolate the cause of medication-NA. Originally, as discussed chapter 1, the FDM considers patient-related (i.e., patient's knowledge, attitude, self-efficacy, beliefs on treatment efficacy, and perceived barriers to adherence), socioeconomic-related (i.e., social networks, family functioning, and the cost of medication), therapy-related (i.e., side-effects of the regimen, duration of treatment, and dose complexity), condition-related (i.e., comorbidities, depression, and other psychiatric diagnoses such as substance abuse), and health care team/system-related factors (i.e., knowledge of healthcare professionals and the relationship between the patient and their healthcare team) for chronic disease groups such as asthmatics, hypertensives, and diabetics (Sabaté, 2003). Unfortunately, the WHO's FDM has not been updated since the early 2000s in response to recent studies on chronic diseases. Given this, I conducted a literature review from recent quantitative studies and systematic reviews to identify these factors that show current trends of medication-NA. A total of 57 studies were identified for the literature review. Appendix A has four matrices for the 57 articles that I used in this literature review. For example, Matrix 1 has 20 medication-NA studies for chronic diseases. Matrix 2 has

another 20 medication-NA articles for cancer studies. Matrix 3 has a total of 16 OET-NA studies for breast cancer and finally Matrix 4 has one non-OET medication-NA research study for breast cancer to investigate determinants of medication-NA.

Patient-Related Factors

Table 2.1

Patient-Related Factors of Medication-NA

Patient related factors	**Sub factors**	Chronic diseases	Cancer	Breast cancer
Psychological	Self-efficacy	Al-Noumani et al. (2016), Bane et al. (2006), Colbert et al. (2013)		Moon et al. (2017)*, Kimmick et al. (2015) Toivonen et al. (2020)
	Belief & concerns	Al-Noumani et al. (2016), Crawshaw et al. (2016)*, Fernandez-Lazaro et al. (2019), Unni et al. (2021)		Moon et al. (2017)*, Brett et al. (2018)
	Depression	Chew et al. (2015), Crawshaw et al. (2016)*	Mathes et al. (2014b)*,Santos et al. (2019)	Yussof et al. (2022)*
	Cognitive (knowledge)	Fernandez-Lazaro et al. (2019), Hussein et al. (2020), Unni et al. (2021)		
	Cognitive (forgetfulnes)	Dennis et al. (2010), Unni et al. (2021)	Hirao et al. (2017)	
Behavioral	Attitudes	Crawshaw et al. (2016)*		
	Eating habits	Mannan et al. (2020), Nonogaki et al. (2019)		
Patient characteristics	Younger ages	Broekmans et al. (2008), Fernandez-Lazaro et al. (2019), Krueger et al. (2015), Molnar et al. (2016)	Dashputre et al. (2020), Geissler et al. (2017), Mathes et al. (2014b)* (n=7 from review)	Brett et al. (2018), Pourcelot et al. (2018)
	Older ages		Grundmark et al. (2012), Mathes et al.	Harrell et al. (2017),

		(2014b)* (n=12 from review), Noens et al. (2009), Timmers et al. (2015)	Yussof et al. (2022)* (n=5 from review)
Ethnic backgrounds (Not being White)	Cedillo-Couvert et al. (2018), Chen et al. (2009), Molnar et al. (2016)	Banegas et al. (2018), Darkow et al. (2007), Halpern et al (2009), Lee & Salloum (2015), Mathes et al. (2014b)*	Sheppard et al. (2019)
Female genders	Mathes et al. (2014a)* (n=6 from review)	Banegas et al. (2018), Clarks et al. (2021), De Figueierdo Jr. et al. (2014), Geissler et al. (2017)	
Male genders	Mannan et al. (2020)	Noens et al. (2009)	Ali et al. (2022)
Low educational level	Fernandez-Lazaro et al. (2019), Hussein et al. (2020), Uni et al., (2021)		

Note. *Systematic review

Table 2.1 lists patient-related factors which affected medication adherence. Three main factors —psychological, behavioral, and patient characteristics— with 13 sub-factors were noted. I will discuss each main factor and introduce subfactors afterwards.

Patient-Related Factors: Psychological

Psychological factors positively associated with medication-NA included disbelief of medications' effectiveness, being in a current state of depression, being prone to forgetfulness, low self-efficacy, and less knowledge of medication administration (Table 2.1). Generally, the psychological factor that is most discussed in chronic disease medication-NA articles are patient beliefs related to taking medication. Patients' perceived beliefs about the medications they are prescribed are a critical factor for adults with chronic disease; more than 20 articles (including the one systematic review) emphasized this factor for patients with diabetes type II and hepatitis C as well as those with kidney-related and cardiovascular-related diseases (see Matrix 1 in Appendix A).

Another important psychological factor is depression, which is noted more frequently in cancer-focused studies than those focused on other chronic diseases (Mathes et al., 2014b; Santos et al., 2019). Furthermore, many articles emphasized that OET-NA in breast cancer patients is especially highly related to psychological symptoms, such as anxiety and depression indicators (i.e., anxiety, depression) and cognitive functioning due to the increased age of the population (Brett et al., 2018; Corter et al., 2018; Fleming et al., 2020; Hershman et al., 2016; Kimmick et al., 2015; Lambert et al., 2018; Toivonen et al., 2020; Yussof et al., 2022).

Cognitive factors (knowledge and forgetfulness) are also significant psychological factors in determining if patients will not adhere to their medication (Fernandez-Lazaro et al., 2019; Hussein et al., 2020; Unni et al., 2021). Even though there is a physiologic aspect to cognitive factors (Coleman, 1985); this study focuses on all cognitive issues under psychology. However, educating patients about cancer medication did not significantly enhance medication adherence (Pourcelot et al., 2018). Embracing and acknowledging cancer patients' psychological factors (i.e., self-efficacy, anxiety, depression) in education materials can encourage them to adhere to medication and a treatment plan (Kaptein et al., 2020). While there is not enough evidence to correlate the link between patient knowledge and medication adherence, there are several studies showing that knowledge may reduce fears of taking medications (Keller et al., 2008; Nizet et al., 2022). Furthermore, forgetfulness is a non-quantifiable or non-modifiable factor that is commonly discussed as a psychological factor regarding unintentional medication-NA (Skrabal Ross et al., 2020). Unni and Farris (2011) demonstrated that forgetfulness is one of the main factors impacting medication-NA. They have also shown that patient beliefs about medication are closely

related to forgetfulness. For example, if patients believed their medication is beneficial for their health, they were more likely to remember to take medications. These findings are linked together and supports how cognitive factors are contributing to medication-NA for chronic disease patients.

When reviewing selected psychological factor focused articles, I found that most of the quantitative studies included small sample sizes. A total of seven selected articles in psychological categories (Table 1) had an average sample size of 1,000 patients in a single site setting (i.e., small clinic or community hospital). While the majority of the selected studies utilized cross-sectional design, there were two studies that used secondary data analysis, and one which was a quantitative systematic review study. Despite the differences in design, all the studies followed these same trends in sample sizes and settings. Even though these studies only have small sample sizes in a single site, I found that the selected studies utilized various types of samples from countries and continents (North America, Europe, Asia, South America, Africa, and Middle East) with diverse ethnic backgrounds to understand the psychological factors of chronic disease including cancer. This suggests that even though the small sample sizes will make our synthesized findings less generalizable, they can still be considered applicable in diverse settings accommodating multiple ethnic backgrounds.

Moreover, theoretical frameworks support researchers to identify and quantify several confusing psychological terms (i.e., self-efficacy, medication belief) to gain a clearer understanding of the abstract nature of psychological related factors. For example, researchers utilized the self-regulation model, theory of planned behavior, and the socio-cognitive theory to understand medication adherence. Specifically, the self-regulation model

can help patients to engage more in their medication-taking behavior from helping them understand their illness correctly (e.g., what the disease is, what it means to the patient, its causes, its consequences, how long it will last, and whether it can be cured and/or controlled) (Browning et al., 2010). However, this self-regulation model did not significantly improve medication adherence compared to other theories in chronic disease patients (Al-Noumani et al., 2016; Nili et al., 2020). Moreover, Bandura's social cognitive theory (1977) focuses on self-efficacy, which is a core social cognitive theory construct that allows patients to change how they feel, think, behave, and motivate themselves through their own confidence in their capability to conduct a specific action towards a specific outcome (Glanz et al., 2015; Zhang et al., 2015). Using the socio-cognitive theory to enhance medication adherence was effective among patients with HIV, hypertension, stroke, and those who have had an organ transplant (Colber et al., 2013; Dobbles et al., 2017; Garofalo et al., 2016; Kamal et al., 2015; Ma et al., 2014). Lastly, the theory of planned behavior was a helpful framework to identify the medication beliefs and cognition, which determine an individual's behavior and self-efficacy (Bane et al., 2006). Several studies demonstrated the theory of planned behavior was helpful to understand medication-NA. However, most of these theoretical frameworks only focused on analyzing patient-related factors (i.e., self-efficacy and other cognitive-psychological related terms) rather than understanding medication-NA as a whole.

Patient-Related Factors: Behavioral

Behavioral factors encompassed attitudes (Crawshaw et al., 2016), and eating habits (i.e., following a special diet, or eating fruits and vegetables for health) (Mannan et al., 2020; Nonogaki et al., 2019). Two studies in chronic disease categorized patients' healthy eating habits as a behavioral factor. Nonogaki et al. (2019) focused on diabetes mellitus patients

following the MoPoTsyo Food Pyramid diet and found that patients on special diets were likely to adhere to their medication. Meanwhile, Mannan et al. (2020) demonstrated that eating habits such as consuming fewer fruits and vegetables showed a significant correlation with medication-NA for patients with ocular disorders and diabetic ulcers. These studies indicated that eating habits can be combined with medication adherence as a positivw behavioral factor and eventually both efforts can increase patients' health outcomes.

Some articles tried to study patients' attitudes directly rather than observing them via other factors (i.e., eating habits). For example, one of the studies utilized the dysfunctional attitudes psychometric scale to measure three aspects of patient attitudes: achievement, dependency, and self-control. These aspects were positively associated with medication-NA (Crawshaw et al., 2016).

In regards to sample and setting characteristics, three selected behavioral factor focused studies used small sample sizes. The two cross-sectional studies and one systematic review study showed the same trend of having less than 2,000 participants in a single site setting. Despite the issues of small sample sizes and localized site settings, samples of behavioral factors were collected in countries with diverse ethnic backgrounds. For example, the selected review study collected their samples from the USA (n=9), Europe (n=6), Israel (n=1), China (n=1), and Argentina and Brazil (n=1) (Crawshaw et al., 2016). In addition, the two selected cross-sectional studies were conducted in Bangladesh and Cambodia, which increased the diversity of samples. It is difficultd to generalize these review findings because of small sample sizes even though these studies had diverse samples across different countries.

Moreover, there were no quantitative cancer-specific studies focused on behavioral factors included in this review. No theoretical frameworks were used in the reviewed cancer studies. Unfortunately, measuring and understanding behavioral factors is still an abstract and difficult concept. Even though many other researchers have been trying to apply the theoretical framework in understanding this work, I was not able to retrieve studies using a theoretical framework to understand behavioral factors in this literature review.

Patient-Related Factors: Patient Characteristic

The last category of factors affecting medication-NA is patient characteristic factors. When looking at patient characteristic factors, age, ethnic background, gender, and education level were the sub-factors most associated with poor medication adherence (Table 1). In patients with chronic diseases, younger age was identified as a factor related to medication-NA; however, the majority of cancer reviews and articles suggested that older age was a determinant for medication-NA in that population. Also, breast cancer patients over 69 years of age in particular had a higher medication-NA than their younger female counterparts (Gieseler et al., 2019; Verbrugghe et al., 2013). Moreover, most chronic disease studies (including those focused on cancers) pointed out that Non-Hispanic Whites are the most adherent ethnic group, with a notable incongruity in the findings of Hiko et al. (2012). Being female is more frequently identified as a factor in medication-NA than being male in chronic disease and cancer patients (Table 1). Still, some studies on diabetic and pain medications showed that being male was associated with medication-NA (Broekmans et al., 2008; Mannan et al., 2020).

Furthermore, having a lower education level is also consistently related to medication-NA in chronic condition patients (Fernandez-Lazaro et al., 2019; Hussein et al.,

2020; Uni et al., 2021). Still, some studies consider lower education level (i.e., less than high school education) a reflection of health illiteracy and/or inability to comprehend patient education pamphlets (Fernandez-Lazaro et al., 2019). However, some chronic disease studies' findings contradicted this and mentioned that education level was not correlated with adherence in patients with pain and hepatitis C (Broekmans et al., 2008; Mathes et al., 2014). Also, there are no apparent cancer-focused studies (including those focused on breast cancer) to show a strong relationship between education level and medication-NA.

Unfortunately, there are several limitations on studies focusing on patient characteristic factors in chronic disease including cancers. No theoretical frameworks were used to understand patient characteristic factors and most of the studies are not easily generalizable due to small-sized and less diverse samples. The majority of the studies had an average sample of around 1,000 participants in a single site setting. A total of seven secondary data analysis studies utilized samples with multi-site setting, their average sample size was 2,000 patients (Cedillo-Couvert et al., 2018; Dashputer et al., 2020; Gissler et al., 2017; Grudmark et al., 2012; Harrell et al., 2017; Lee & Salloum, 2015; Sheppard et al., 2019). Moreover, samples were collected from the U.S.A, Europe, and Asia, but there is considerably more data from the U.S.A. This may have skewed the findings since many of the studies were conducted in the U.S.A. The studies are also lacking samples from South America, the Middle East and Africa. These findings are hard to generalize due to small and less diverse samples across different countries.

Socioeconomic-Related Factors

Table 2.2

Socioeconomic-Related Factors of Medication-NA

Socioeconomic related factors	Sub factors	Chronic diseases	Cancer	Breast cancer
Social/environmental factors	Decreased social support	Crawshaw et al. (2016)*	Mathes et al. (2014)*	Moon et al. (2017); Lebovits (1990)**
	Decreased cohabitation status	Molnar et al. (2016)	Geissler et al. (2017)	Mohamed & Elamin (2020)
Economic factors	Financial constraints	Adidija et al. (2018), Chew et al. (2015), Dennis et al. (2010), Hussein et al. (2020), Mannan et al. (2020), Nonogaki et al. (2019)	Al-Dewik et al. (2016), Streeter et al. (2011)	Lebovits (1990)**
Lifestyle factors	Alcohol and drug use	Fernandez-Lazaro et al., (2019); Mathes et al. (2014), Nonogaki et al. (2019)		

Note. *Systematic review **breast cancer with non OET medication study

Table 2.2 lists socioeconomic factors which affected medication adherence. Three socioeconomic factors were noted: social/environmental, economic, and lifestyle factors. These were then divided into four sub-factors. I will discuss each main factor and subfactor in detail below.

Socioeconomic-Related Factors: Social/environmental

When looking at social/environmental factors, social support and marital or cohabitation status were associated with poorer medication adherence. Every study I reviewed demonstrated that a lack of social support typically leads to medication-NA in chronic disease and cancer patients. Some studies found that social support from family, friends and other survivors is one of the significant factors contributing to OET adherence for

breast cancer patients (Moon et al., 2017). This is because care and support from significant others can improve patients' poor mental resilience, and even restore their normal psychological state (Xu & Wang, 2019). Greater social support at prescription initiation was strongly associated with lowering psychological symptoms such as depression (Bright & Stanton, 2018; Toivonen et al., 2020).

Moreover, marital or cohabitation status is one of the essential factors influencing medication-NA (Geissler et al., 2017; Mohamed & Elamin, 2020; Molnar et al., 2016). When they are married, breast cancer patients have a lower OET-NA because there is a higher chance that their significant other will remind, and encourage the patient to take their OET medicine, sometimes even taking it upon themselves to administer it. However, the divorce rate is as high as 52% after breast cancer related surgeries, and studies show an increase in depression and anxiety among these divorced breast cancer patients (Xu & Wang, 2019). Of the studies reviewed, it is important to note that the study by Tan et al. (2017) was the only study that demonstrated marital status was not associated with OET- NA among breast cancer patients. However, their results may differ because they included more diverse samples which may be skewed by specific populations' cultural influences, such as paternalism or condescension (Kaye, 2016; Tan et al., 2017).

Regarding the limitations of the selected studies, no theoretical frameworks were recognized. Most studies demonstrated an average sample size of about 500 patients in a single site setting. However, there was one study that had a notably bigger sample: 32,348 U.S. veterans in a multi-site setting (Molnar et al., 2016). All of these selected studies showed that decreased social support is recognized as a significant social/environmental factor, even with different samples and settings. However, most studies were conducted in

the U.S.A and Europe without considering samples with diverse ethnic backgrounds. For example, Molnar et al. (2016) demonstrated that their secondary data-analysis samples were 74% White, 23% African American, and 3% other races due to the uneven race enrollment in U.S. veteran services. Overall, these results of samples in selected studies are hard to generalize in other race groups and/or countries since the diversity of the samples did not reach optimum status.

Socioeconomic-Related Factors: Economical

More chronic disease articles emphasized financial constraints as a factor for medication-NA than cancer studies; these trends were the same across countries such as Cameroon, India, Japan, and the U.S. (Adidja et al., 2018; Clarks et al., 2021; Dennis et al., 2010; Hirao et al. 2017). Even though there was a similar medication-NA pattern with financial constraints in cancer studies (including breast cancer), there were several contradicting trends concerning financial constraints that appear in breast cancer studies. Some studies showed that low-income was not associated with OET-NA among older female breast cancer patients (the mean age of the sample was 67.7 years old) (Fleming et al., 2022; Weaver et al., 2013). However, review studies that did not consider patient age showed that financial status (i.e., low income) is one of the most significant factors contributing to medication-NA in breast cancer patients (Lebovtis et al., 1990).

Even though there is inconsistency in the findings, it is known that older cancer patients and minority populations with cancer are more vulnerable because they tend to have limited income. Similarly, there is a positive association between ethnic minority group and medication-NA because of limited financial resources. Lee and Salloum (2015) presented findings that older, lower income African American and Hispanic cancer patients were more

likely to have higher medication-NA compared with non-Hispanic Whites with higher incomes. This example showed that financial constraints are interrelated with ethnic background and in influencing medication-NA.

Regarding the limitations of the selected studies, no theoretical frameworks were recognized, and less diverse and small samples were found. Among the 10 selected studies on understanding economical factors, most studies were utilizing cross-sectional design with small sizes of samples (average sample size = 865 patients) in single site settings. One study applied secondary data analysis of 2,000 patients but utilized a single site rather than multi-site settings (Hussein et al., 2020). Interestingly, the selected samples were mostly collected in developing countries such as Cameroon, Malaysia, India, Egypt, Cambodia, and Bangladesh. Only two studies utilized samples from the U.S.A and Middle East. Because selected samples were more focused on specific populations and developing countries, the samples were not as diverse enough in this literature review. Overall, the economical factors cannot be generalized due to small and less diverse samples.

Socioeconomic-Related Factors: Lifestyle

Three studies identified using alcohol and drugs as a lifestyle factor (Fernandez-Lazaro et al., 2019; Mathes et al., 2014; Nonogaki et al., 2019), but only Nonogaki et al. (2019) showed using alcohol and drugs as a significant factor for medication-NA (specifically while studying diabetic patients in Cambodia). I did not identify any cancer studies that demonstrated a strong relationship between this factor and medication-NA in cancer patients specifically (Mislang et al., 2017; Verbrugghe et al., 2013).

Regarding the limitations of the selected studies, no theoretical frameworks were recognized, and less diverse and small samples were utilized to understand lifestyle factors in

chronic disease. All of these selected studies were either cross-sectional studies or the review studies. The average sample size was 500 patients in a single site setting (Fernandez-Lazaro et al., 2019; Mathes et al., 2014, Nonogaki et al., 2019). Unfortunately, sample were not diverse enough to conclude this lifestyle factor was significant because most of results came from U.S.A. and Europe (Fernandez-Lazaro et al., 2019; Mathes et al., 2014). Overall, these results demonstrated that samples were not diverse and large enough to generalize my review findings.

Therapy-Related Factors

Table 2.3

Therapy-Related Factors of Medication-NA

Therapy related factors	Sub factors	Chronic diseases	Cancer	Breast cancer
Medication effects	Side-effects	Adidja et al. (2018), Chew et al. (2009)	Noens et al. (2009)	Brett et al. (2018), Fleming et al. (2022)*, Harrell et al. (2017), Murphy et al. (2012)*, Toivonen et al. (2018)*, Yussof et al. (2022)*, Lebovits (1990)**
Medication regimen	Polypharmacy	Hussein et al. (2020)	Mathes et al. (2014b)*	
	Concomitant medications		Clarks et al. (2021), Geissler et al. (2017)	
	Increased dose of medications	Mathes et al. (2014a)*	Darkrow et al.,2008; Geissler et al. (2017), Noens et al. (2009)	Lebovits (1990)**

	Additional therapy	Molnar et al. (2016)	Dashputre et al. (2020), Hirao et al. (2017)	Yussof et al. (2022)*
	Types of medications		Banegas et al. (2018), Broekmans et al. (2008), Geissler et al. (2017), Marques & Pierin (2008), Streeter et al. (2011)	
	Duration of medications		Banegas et al. (2018), Marques & Pierin (2008), Noens et al. (2009)	Yussof et al. (2022)*
	Switching medications		Marques & Pierin (2008)	Murphy et al. (2012)*, Yussof et al. (2022)*

Note. *Systematic review **breast cancer with non OET medication study

Table 2.3 lists therapy-related factors which affected medication adherence. Medication effects and medication regimens were identified as the overarching therapy-related factors, which were then divided into eight sub-factors.

Therapy-Related Factors: Medication Effects

On the topic of medication effects, side-effects are frequently discussed throughout all the selected articles. In chronic disease, Adidja et al. (2018) stated that multiple daily doses, and side-effects of drugs were positively associated with NA for hypertensive patients. Furthermore, multiple studies in this review show that side-effects are a more significant factor for medication-NA among breast cancer than other cancer or chronic disease. However, Fleming et al. (2022) demonstrated that even though side-effects have positive relationships with medication-NA, this seems to be a short-term problem. Although knowledge of potential side-effects may cause a patient not to want to start taking a new medication, they typically will continue to take medications as recommended once they have

started. This indicates that even if breast cancer patients initially resist taking a medication due to its side-effects, once they are taking the medication, they tend to take it consistently for the prescribed period of time without discontinuing the medication abruptly.

In terms of the limitations of the selected studies, no theoretical frameworks were recognized in the selected studies to understand medication effects. Most studies were using cross-sectional design with an average sample of 500 patients in single site settings in the U.S.A. and Europe. Overall, these results are hard to generalize due to smaller and less diverse samples.

Therapy-Related Factors: Medication Regimen

Medication regimen factors are the most significant factors for general cancer patients (with lower significance for breast cancer patients specifically) (Table 2.3). Polypharmacy, which is defined as the simultaneous use of multiple medication to treat their disease condition, is noted as a factor that increases medication-NA in chronic disease patients (Bakaki et al., 2018). Hussein et al. (2020) stated that polypharmacy tends to be a medication-NA factor for hypertensive patients. Their team reported that there is a positive association between medication-NA and the number of pills a patient has to take. Reasons for this trend include that a lower number of medications is easier for a patient to remember to take and that fewer medications typically lead to fewer side-effects, which in turn leads to greater adherence (Hussein et al., 2020). These trends were reported in cancer patients as well (Mathes et al., 2014b). Moreover, two studies identified that prescribing concomitant medications, which involves taking two or more drugs at the same time, also contributes to medication-NA (Clarks et al., 2021; Geissler et al., 2017). This factor is similar to that of

polypharmacy however, studying concomitant medications specifically focuses on how having to take multiple medications at the same time which may create more medication-NA.

Similarly, increased doses of medications are noted across the studies in chronic disease, cancer, and breast cancer as another factor of medication-NA (Darkrow et al., 2008; Geissler et al., 2017; Lebovitis, 1990; Mathes et al., 2014a; Noens et al., 2009). More cancer studies included this factor as a significant medication-NA determinant than chronic disease studies. For example, prescribing a higher dose of a cancer medication (i.e., imatinib) was strongly associated with medication-NA (Darkrow et al., 2008; Noens et al.,2009).

Furthermore, several studies reported that there is a positive relationship between medication adherence and receiving additional therapy. Especially for breast cancer patients, receiving radiotherapy, surgical therapy, and/or other chemotherapy before starting OET led to greater adherence (Blanchette et al., 2020; Yussof et al., 2022).

In the medication regimen category, types of medication, switching of medications, and duration of medication usage were the significant factors for medication-NA in cancer patients especially. Different types of cancer medications can lead to different levels of medication-NA. Switching medications or providing alternative treatments is one of the most effective methods for combating medication-NA in cancer patients (Harrell et al., 2017; Marques & Pierin, 2008; Murphy et al., 2012). For example, if a patient was changed from tamoxifen to AI treatment, OET-NA decreased (Font et al., 2012; Gao et al., 2018; Lailler et al., 2021; Murphy et al., 2012; Yussof et al., 2022). However, if a patient was switched from AI to tamoxifen, OET-NA increased compared to patients taking AI alone (Lailler et al., 2021). These findings suggest that taking tamoxifen may cause higher OET-NA than taking AI. Also, the timing of the switch is important. Switching medications late in treatment

causes higher OET-NA compared to switching earlier in breast cancer populations (Trabulsi et al., 2014; Yussof et al., 2020). In addition to carefully considering which medications a provider selects for a change in regimen, duration of medication usage was also reported as a critical factor for medication-NA. Noens et al. (2009) demonstrated that if patients are on cancer medication (i.e., imatinib) for a longer period of time, they are more prone to medication-NA. These trends were the same in breast cancer. For example, the rate of OET adherence tends to drop as time goes on because patients are typically prescribed this medication for a span of 5-10 years (Yussof et al., 2022).

Unfortunately, several limitations were noted on the studies focusing on medication regimen factors. No theoretical frameworks were used to understand medication regimen factors and samples sizes were small and less diverse ethnic groups; making it difficult to generalize my review findings. All of the studies had less than 1,000 participants in a single site setting, except several secondary data analyses. Moreover, many studies were conducted in the U.S.A, and Europe without considering diversity of sample characteristics. Overall, these results may increase the bias of my review findings.

Condition-Related Factors

Table 2.4

Condition-Related Factors of Medication-NA

Condition related factors	Sub factors	Chronic diseases	Cancer	Breast cancer

Disease control factor	Symptoms	Bane et al. (2006), Chen et al. (2009)	De Figueierdo Jr. et al. (2014), Hirao et al. (2017), Noens et al. (2009)	Kimmick et al. (2015)
	Severity		De Figueierdo Jr. et al. (2014), Darkow et al., (2007)	Inotai et al. (2021)
Disease characteristics	Time since diagnoses	Gast & Mathes, (2019)	Noens et al. (2009)	Murphy et al. (2012)*
Comorbidities		Cedilio-Couvert et al. (2018), Crawshaw et al. (2016)*, Hussein et al. (2020), Mannan et al., (2020), Mathes et al. (2014a)*, Nonogaki et al. (2019)	Dashputre et al. (2020)	Pourcelot et al. (2018), Yussof et al. (2022)*

Note. *Systematic review

Table 2.4 lists condition-related factors which affected medication adherence. Three condition-related factors (disease control factors, disease characteristics, and comorbidities) with four sub-factors were identified. I will discuss main factors and the following sub-factors of condition-related determinants.

Condition-Related Factors: Disease Control

The sub-factors of disease control are symptoms and severity of disease. Bane et al. (2006) demonstrated that experiencing symptoms (i.e., headaches, dizziness) of hypertension are positively associated with medication-NA. These trends of experiencing symptoms influencing medication-NA in chronic disease patients were similar in cancer studies. Cancer patients tend to have higher medication-NA when they are experiencing bothersome

symptoms (i.e., dyspnea, diarrhea, pain) from cancer (Table 2.4). More severe illness (i.e., advanced stage of disease, recurrences of cancer, metastasis of cancer) is also correlated with higher medication-NA. This particular trend has only been recorded in cancer populations (Inotai et al., 2021). For example, Darkrow et al. (2008) demonstrated that high cancer complexity/severity was likely to be associated with medication-NA. This trend works the same in breast cancer patients. Advanced breast cancer stage patients with metastasis (i.e., Stage 4) tend to have a higher OET-NA (Bosco-Levy et al., 2016; Guedes et al., 2017; Yussof et al., 2022). However, non-metastatic breast cancer patients have a higher OET adherence rate, despite higher tumor grade and more lymph node involvements, compared to patients in earlier stages of breast cancer (Hagen et al., 2019; Wulaningsih et al., 2018; Yussof et al., 2022). Interestingly, some studies found that the cancer severity is not correlated with medication-NA. For example, in chronic myeloid leukemia patients there was no significant relationship between adherence and phase of disease (Geissler et al., 2017).

I have found several limitations on the studies focusing on disease control factors. There were no theoretical frameworks used to understand these factors and they utilized a less generalizable sample quality. Most of the studies had less than 1,000 participants in a single site setting. However, the selected studies were conducted in Brazil, Taiwan, Europe, South Korea, Japan, New Zealand, Canada, and the U.S.A, making them more diverse than the other studies I have reviewed. However, it is still hard to generalize the findings with the small sizes of the samples.

Condition-Related Factors: Disease Characteristics

Under disease characteristics, time since diagnosis was a subfactor that is positively related with medication-NA (Murphy et al., 2012; Noens et al., 2009). For example, a cancer

patient diagnosed five years ago will tend to have higher medication-NA than a patient who was diagnosed within the last year. These trends are also consistent with findings from studies in patients with chronic illnesses; for instance, patients who have been suffering with diabetes for a longer period had higher medication-NA (Gast & Mathes, 2019).

Regarding the limitations of the selected studies, no theoretical frameworks were recognized, less diverse ethnic groups were studied, and small samples were used to understand disease characteristics factors. Most selected studies were either cross-sectional studies or review studies. From the selected studies, the sample size was usually less than 500 patients in a single site setting and collected mostly from the U.S.A. and Europe (Gast & Mathes, 2019; Murphy et al., 2012). Overall, my review results are hard to generalize because samples were not diverse or large enough to conclude the findings.

Condition-Related Factors: Comorbidities

Comorbidities were all positively related with medication-NA in any chronic disease population throughout all the studies I reviewed; however, more articles are found in chronic disease than in cancer (Table 2.4). This is because non-cancer chronic diseases affect a patient's entire body. For example, diabetic disease influences the entire body compared to non-metastatic cancer by circulating in blood systems with increased blood sugar (Schrijvers et al., 2004).

Some studies showed a positive relationship between medication-NA and comorbidities in general instead of identifying specific comorbidities that impacted medication-NA (Dashputre et al., 2020; Yussof et al. 2022). Other studies identified strokes, cardiovascular disease (CVD), diabetes, and dyslipidemia as important comorbidities for cancer patients (Cho et al., 2018; Zullig et al., 2022). Specifically, cancer patients with CVD

or CVD risk factor-related comorbidities (i.e., diabetes, hypertension, and dyslipidemia) had a lower medication adherence in general, and their medication adherence may decline over time (Zullig et al., 2022). This indicates that understanding comorbidities is one of the most critical factors for medication adherence.

In regard to the limitations of the selected studies, I could not identify theoretical frameworks, nor generalizable samples to understand comorbidity factors. Selected studies were cross-sectional studies, secondary data analyses, or review studies. The sample sizes were mostly less than 1,000 patients and samples were mostly collected from the U.S.A. and Europe. Overall, these results demonstrated that the samples were not diverse or large enough to generalize my review findings.

Health care Team/System-Related Factors

Table 2.5

Health Care Team/System-Related Factors of Medication-NA

Healthcare team/system related factors	Sub factors	Chronic diseases	Cancer	Breast cancer
Health care team factor	Relationship and Interaction		Geissler et al. (2017), Marques & Pierin (2008)	Moon et al. (2017)*, Toivonen et al. (2020)*, Kimmick et al. (2015), Lebovits (1990)**
	Provider's experience (years)		Noens et al. (2009)	
	Not seeing or no referral to specialist			Murphy et al. (2012)*

Health care system factor	Less number of healthcare services	Fernandez-Lazaro et al. (2019), Hussein et al. (2020), Nonogaki et al. (2019)	Al-Dewik et al. (2016), Dashputre et al. (2020), Halpern et al. (2009), Noens et al. (2009)	Yussof et al. (2022), Tan et al. (2017)
	Type of insurance		Dashputre et al. (2020), Lafeuille et al. (2014)	Sheppard et al. (2019), Tang et al. (2018)*
	Increased cost	Chen et al. (2009)	Halpern et al. (2009), Mathes et al. (2014b)*, Streeter et al. (2011)	Murphy et al. (2012)*

Note. *Systematic review

Table 2.5 lists health care team/system-related factors which affected medication adherence. Two therapy-related factors (healthcare team factors and healthcare system factors) with four sub-factors were identified. I will review two major factors and sub factors below.

Health Care Team Factors

Under the healthcare team factors, there is one sub-factor: relationships and interactions. Only cancer-focused studies discussed this factor, and it was especially emphasized for breast cancer populations (Lebovits, 1990; Moon et al., 2017; Toivonen et al., 2020). Some studies discovered that patients with chronic disease feel unable to discuss their medication concerns with healthcare providers due to a limited trust-based patient-provider communication relationship. This situation may be caused by patients feeling unheard or having assumptions about their providers and can negatively impact the self-efficacy of patients (Lambert-Kerzner et al., 2015; Marques & Pierin, 2008). The same trends were also recognized in cancer studies. Good patient–physician relationships are major contributors to medication adherence for female breast cancer patients and positive

interactions between patient and healthcare professionals can support medication adherence (Lin et al., 2017; Moon et al., 2017). For example, the study by Ma et al. (2020) found that there is a trend of increased OET-NA over five-year treatment periods when patients are introduced to take generic AI by healthcare providers due to a general distrust of generic medications. However, the study also showed that patients who have strong relationships with their healthcare providers will be more likely to adhere to the generic medication because of the trust they have in their provider. Moreover, sharing in decision-making with healthcare professionals (e.g., personalizing care plan) are associated with better OET adherence (Yussof et al., 2022). Unfortunately, many cancer patients are suffering from insufficient treatment due to working with less-experienced providers and/or not being referred to specialists. This often leads to a discontinuation of care (Murphy et al., 2012; Noens et al., 2009).

Several limitations are found in the selected studies focusing on healthcare team factors. Firstly, there was no theoretical framework to understand these factors. Most selected studies were quantitative review studies. Even though their sample sizes were mostly less than 1,000 patients and samples were collected across different countries, such as Brazil, America, the Near and Middle East, Asia, and Europe. Overall, these results demonstrated that the samples were diverse but not large enough to generalize my review findings.

Health Care System-Related Factors

In health care systems such as the one in the United States, Mathes (2014b) found that higher co-payments with Medicare or private insurance always positively impacts medication-NA, especially for patients with inflammatory arthritis, and cardiovascular related diseases. Higher out-of-pocket costs for OET was positively associated with higher

OET-NA (Bosco-Levy et al., 2016; Ma et al., 2020; Yussof et al., 2022). Less frequent use of healthcare services (i.e., hospitalization, pharmacy visits) was positively associated with higher OET-NA as well (Yussof et al., 2022). This indicates that patients who use healthcare services more often tend to adhere better to their medication. Moreover, continuing care in the same hospital is associated with better OET adherence (Yussof et al., 2022).

For limitations of the studies on the healthcare system-related factors, I have found that there was no theoretical framework used to understand this factor. Moreover, sample sizes were not large or diverse enough to generalize my review findings. All selected studies were cross-sectional studies with sample sizes of less than 1,000 patients, except several secondary data analyses. Also, most samples had a considerable majority of the data collected from the White ethic group (especially coming from Europe and the U.S.A.) and were lacking samples from Asia, South America, the Middle East and Africa. Overall, these findings are hard to generalize due to small and less diverse samples across different countries.

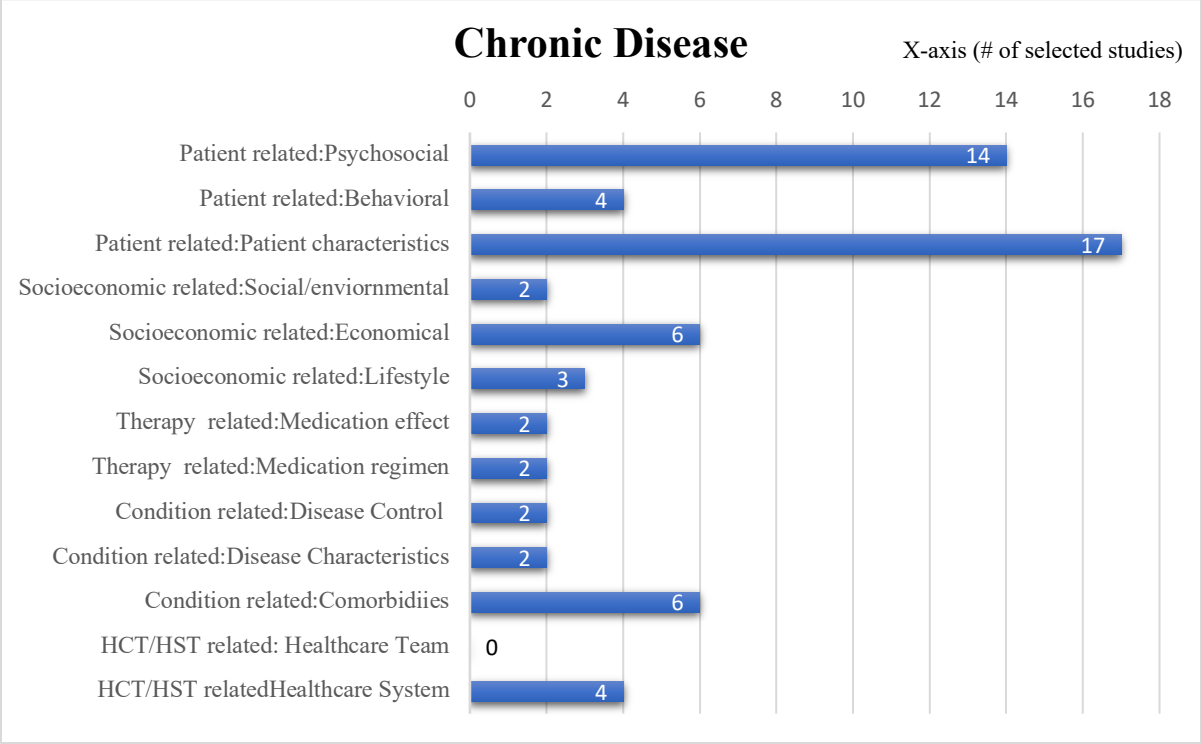
Discussion

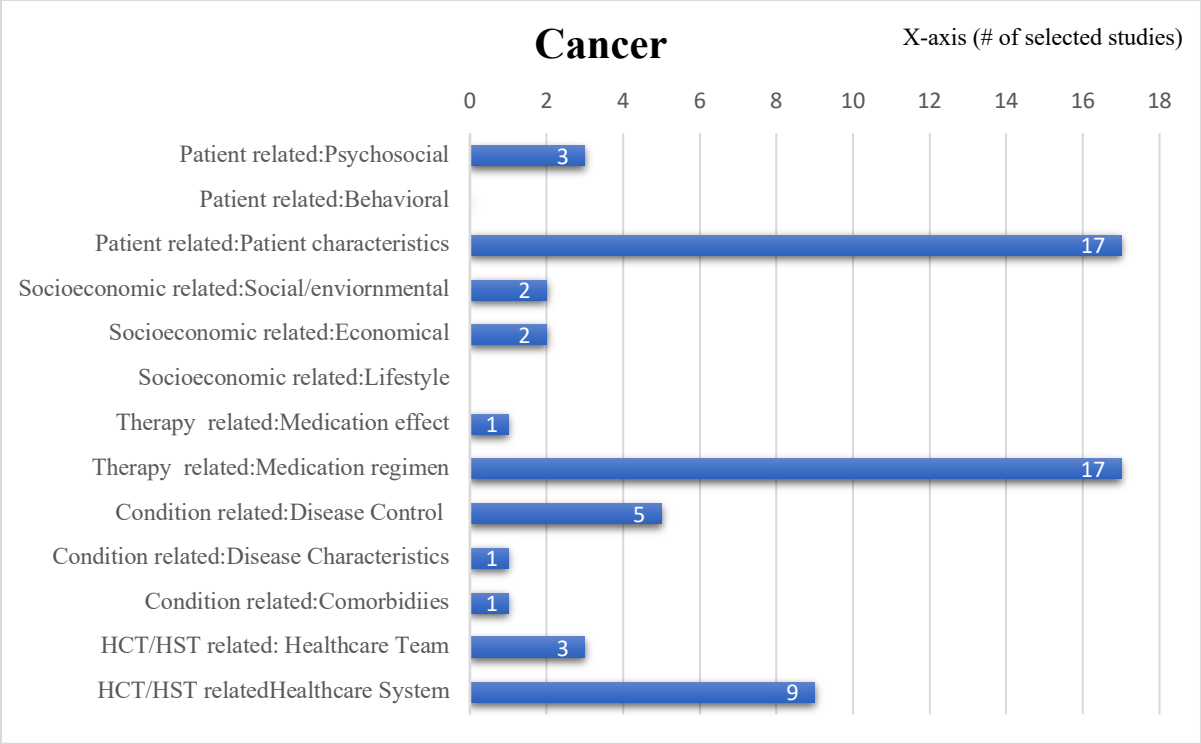
I have created the following histograms (Figure 2.1) to better visualize how all the various factors that have been discussed in this chapter work together. Using this particular style of graph allowed me to separate the major factors (patient-related, socioeconomic related, therapy related, condition related, and healthcare team and system related factors) from their subfactors (13 factors listed in Figure 1). Each different level of specificity of study are listed on the top of the histogram: chronic disease, cancer, and breast cancer specifically. The unit of X-axis is the amplitudes for each factor, in this case being equal to

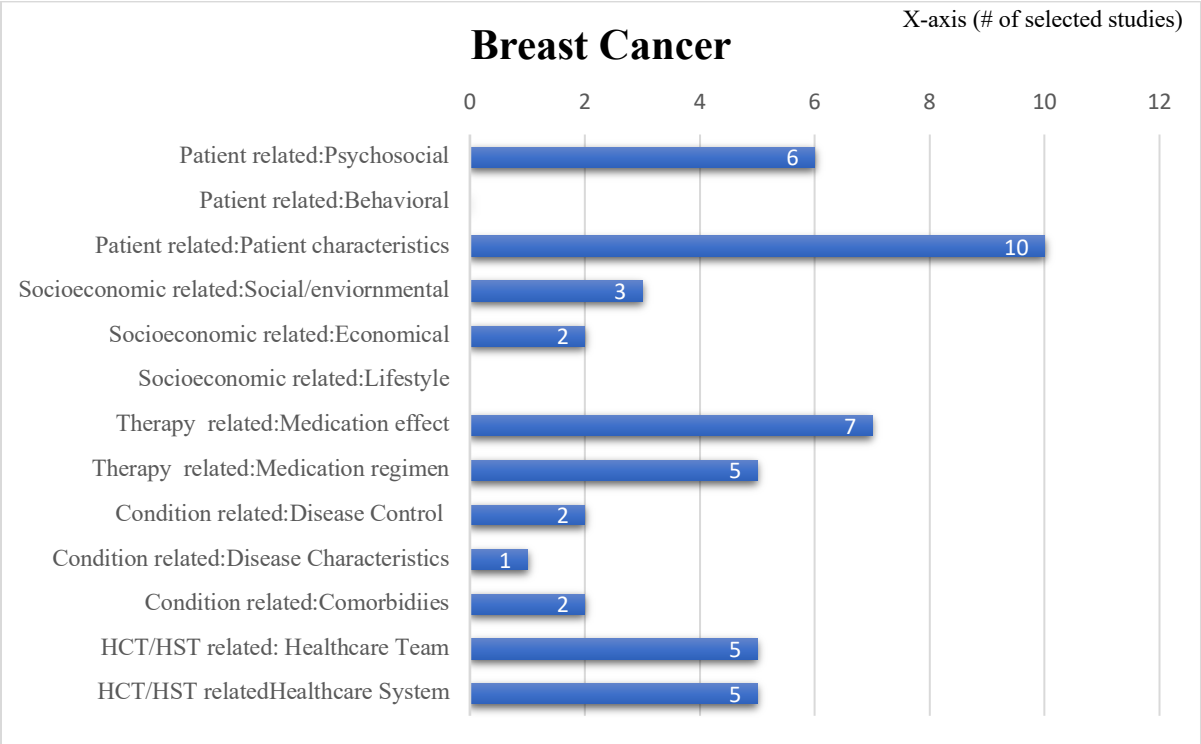
the number of selected studies focused on that factor. The Y-axis or each bar represents one of the subfactors. At the end of the bar has the number, which is X-axis amplitude.

Figure 2.1

Histograms of Medication-NA in Chronic Disease, Cancer, Breast Cancer







*HCT/HST = Healthcare team/system

Being female was identified as a factor for medication-NA throughout the studies on chronic disease (including cancer-focused studies), as shown by the large bars for patient characteristics in each of the histograms (Figure 1). The most surprising trend was the age factor in patient characteristics; unlike most populations, older age cancer patients were less likely to adhere to their medication. Overall, the factors that lead medication-NA in non-cancer chronic disease studies are: (a) younger age, (b) not being from a White ethnic background, (c) having comorbidities, (d) having cognitive and psychological factors, and (d) having financial constraints. Along with gender, age and ethnicities fall into the patient characteristic factors. As shown by Figure 1, having comorbidities, cognitive and psychology factors, and/or financial constraints are all more of a factor for chronic disease patients than for cancer patients (including breast cancer patients). Cancer studies on the other hand demonstrated that: (a) older age, (b) having side-effects, (c) type of medication, and (d) dosage and duration of medication are special factors for medication-NA in this population. In breast cancer populations in particular, having side-effects are most strongly correlated with OET-NA. This is reflected in the fact that the histogram for cancer studies shows a large bar for medication regimen factors and a small bar for medication effects, while the opposite is true for breast cancer studies (Figure 1).

Additionally, I have found several gaps in the research on medication-NA in chronic disease populations including cancer patients while preparing this state of science review. Most of the existing research has been conducted in the U.S. and Europe using single-site samples (N=100-2,000) from small clinics and hospitals (see Matrix1, 2, and 3). Similarly, many retrospective studies examining medication-NA rates have utilized small electronic databases with sample sizes fewer than 10,000 individuals globally (Blanchette et al., 2020;

Harrell et al., 2017; Huiart et al., 2013; Hwang et al., 2020; Murphy et al., 2012; Sella & Chodick, 2018). This trend is also consistent for studies focused on older women with breast cancer in the U.S. Moreover, fewer studies have been conducted with diverse samples (i.e., including various races, ethnicities, genders, age groups, etc.), with especially limited numbers of older American women with breast cancer, even though they are a high risk population (Given & Given, 2016). Unfortunately, many retrospective studies use single-site small sample sizes from small clinics and hospitals, which limit the generalizability of research findings and emphasize the value of future research examining OET-NA rates across diverse sample populations and over multiple site settings.

Moreover, another gap was a lack of theoretical frameworks to explain medication-NA. While there were three studies out of 57 included in this review that acknowledge certain theoretical frameworks (the self-regulation model, the theory of planned behavior, and the socio-cognitive theory) for understanding more abstract factors affecting medication-NA. Still, there remains a gap in the literature when it comes to a multi-level perspective. Even though researchers agree that medication adherence is a complex problem that is influenced by multiple environments, the majority of existing literature focuses on patient-level factors affecting medication adherence (i.e., cognitive and psychological barriers) rather than focusing on multi-level influences (see Matrices 1, 2 and 3). Presently, there are only two research studies out of 57 examining the effects of multi-level influences on OET-NA in older female breast cancer patients in the United States. However, these two studies utilized the multi-level WHO FDM model in a very general manner rather than focusing on each individual factor. This is concerning because medication-NA is a complex issue and the types of theoretical frameworks that could help us to better understand it are largely being ignored

in the current literature. Berben et al. (2012) recommends that health care researchers should use a multi-level ecological perspective, such as Bronfenbrenner's EST, to understand the complexities of medication adherence because medication-NA is frequently due to a combination of multi-level determinants (divided in EST into individual, micro-, meso-, exo-, and macro levels of influences). My literature review shows the potential benefits for using the EST to understand medication-NA. I believe that this review proves that there were several interrelated factors (i.e., patient's ethnic background and socioeconomic factors) which support the EST concept of interconnection.

Conclusion

Even though breast cancer is the most common cancer diagnosed in women, and it is the second most common cause of death from cancer among women in the world, we still do not know the exact rate ranges of OET-NA, or its influencing determinants. Unfortunately, many breast cancer patients, including older individuals, suffer from OET-NA with recommendations for long-term therapy regimens. The recommended regimen for OET is five years; however, Eraso et al. (2021) are now recommending that timeline be doubled to 10 years due to the benefit of lowering risk of late recurrence and death. Considering the high OET-NA with the five-year regimen, it will be even more critical to understand and identify OET-NA determinants to support breast cancer patients' extended treatments so that the new regimens can be effective.

Medication-NA is a complex problem that is simultaneously influenced by multiple factors, and frequently compromised by more than one barrier. The WHO's FDM is a helpful multidisciplinary approach to understanding each determinant's influence on medication adherence (i.e., patient-related, socioeconomic-related, therapy-related, condition-related,

and health care team/system-related factors). I have reviewed these factors on patients with chronic diseases, cancer, and breast cancer to foreground my RESILIENT study, and shown how factors are different for specific populations. From reviewing current literature, I have identified there are some similar and some different trends in medication-NA factors, depending on the specific diseases. For example, most factors were following similar trends except gender, age, side-effects, and medication regimen determinants (see Figure 1). Also, several gaps are found in the current review, such as failure to utilize large, diverse samples from multi-site data sets, and disregarding the role multi-level determinants exert on medication-NA.

My literature review verified that multi-level systems is helpful theoretical framework to identify medication-NA factors as a whole picture. I will use a multi-level influenced theoretical model such as the WHO's FDM in a large sample of older American women with breast cancer to understand this issue and reveal the multi-level factors affecting medication adherence in this population that are currently missing from the literature. Identification of these multi-level determinants will allow the development of tailored interventions in older women with breast cancer.

CHAPTER 3

METHODS

This chapter aims to present the methods of the RESILIENT study. The purpose of this study was not hypothesis testing; instead, this is an exploratory data analysis to identify the rate of OET-NA using large data sets.

Design

This study is a retrospective, descriptive, correlational study investigating OET-NA rates and the multi-level factors influencing OET-NA in women with breast cancer. Secondary data analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database examining OET-NA in the 10-year period following initial cancer diagnosis was performed (SEER, 2022b).

Sample and Setting

The study sample was collected consecutively from the SEER-Medicare database with inclusion and exclusion criteria.

SEER Medicare Database

The SEER program, a clinical database funded by the National Cancer Institute (NCI), collects data on cancer incidence and survival from U.S. cancer registries (SEER, 2022b). The SEER registry contains more than 9 million cancer cases with over 470,000 new cases added to the database every year (Daly & Paquette, 2019). The SEER-Medicare data follows Health Insurance Portability and Accountability Act (HIPAA) requirements with investigators' signed data use agreement (SEER, 2022b). The SEER-Medicare's data collection originally began on January 1, 1973, and covers numerous groups and regions, such as Alaskan natives and Arizona Indians as well as residents of Connecticut, Iowa, New

Mexico, Utah, Hawaii, Georgia, Idaho, Louisiana, New Jersey, Puerto Rico, California, Utah, New York, Massachusetts, Wisconsin, Kentucky, Texas, Michigan, Washington, and Illinois (SEER, 2022b). Murphy et al. (2013) reported that the SEER database represents approximately 30% of the US population. Medicare is federally funded public health insurance, and it is used by approximately 97% of Americans aged 65 years or older (Engels et al., 2011). The SEER database has been linked to Medicare data that includes (a) claims-based measures of comorbidities, (b) screenings and evaluation tests, and (c) detailed treatment and outcomes data, with a collaborative effort by the NCI, SEER registry, and the Centers for Medicare and Medicaid Services (CMS) (Warren et al., 2002). SEER-Medicare is a robust database that includes various populations to cover health disparities, quality of care and cost of treatment in oncologic diseases (Daly & Paquette, 2019). The SEER registry is broadly representative of the US population, although there are some differences (Daly & Paquette, 2019). For example, the database shows different percentages for urban/rural population distribution as well as racial demographics. Specially, the SEER database has a largest racial patient population of US Native Hawaiian/Pacific Islander (who make up 0.3% of the national population according to the most recent census data) while whites (59.3% of the population according to the most recent census data) only make up 23.4% of the database patients. Similarly, black patients are represented almost equally in the database to whites (22.7% to 23.4% respectively) while blacks make up 13.6% of the national population (45.7% less than whites) (Daly & Paquette, 2019; SEER, 2022b; US Census Bureau, 2022). Nonetheless, the SEER-Medicare database is the best cancer database and includes the closest representation of the US cancer population with diverse ethnic groups in a large-size data set with yearly follow-up.

Inclusion Criteria

The cohort selection inclusion criteria are (a) American women, 65 years of age or older, who are enrolled in Medicare Part D, (b) diagnosed with breast cancer stages I-III using ICD-9 174 (10 codes) and ICD-10 C50 (female, 36 codes) from 2010-2019 for OET-NA rates and 2019 for OET-NA determinants, and (c) prescribed one of the following oral medications: tamoxifen, anastrozole, exemestane and letrozole.

Measures/ Instruments

Current literature trends regarding measuring medication adherence demonstrated that the most effective tools are indirect objective methods (as opposed to direct subjective methods) due to better financial benefits and a quicker process. Within this category, utilizing secondary data analysis in medication adherence measurements is one of the most powerful methods, because of easy access to bigger samples without time constraints. The majority of previous secondary data analysis studies used MPR and PDC as a measure for medication adherence. However, I used the PDC for this study because PDC is more recommended than any other measure by the Pharmacy Quality Alliance.

The predictor variables are the multi-level determinants, which are identified by the WHO's FDM— including patient-related, condition-related, therapy-related, social/economic-related, and health care team/system-related factors— correlated to OET-NA. These multi-level variables are adjusted and defined based on the current literature of OET-NA factors based on Chapter 2 in this dissertation. All these variables are able to be located in the SEER-Medicare database, and the detail codes are described in Tables 6 and 7 (SEER, 2022b). The main outcome variable is OET-NA. No questionnaires or instruments were utilized in this study.

The following data definitions were utilized for the multi-level determinants and outcome measures in this study, including patient-related, condition-related, therapy-related, social/economic-related, health care team/system-related factors correlated with OET-NA. Please see Tables 6 and 7 for all the variables and related code files in the SEER-Medicare database.

Multi-level Determinants and Outcome Variables

Multi-Level Determinants

Patient-Related Variables. The patient-related determinant data includes (a) demographic information (age at diagnosis, sex, race, ethnicity, and marital status); (b) psychosocial factors (mental illness such as dementia or depression diagnosis, antidepressant use, memory issue), and (c) behavioral factors (attitudes from past drug management/therapy problems-adherence, eating habits/diet preferences) (Finitsis et al., 2019; Lambert et al., 2018; Lin et al., 2017; MacDonald et al., 2018; Moon et al., 2017; Paranjpe et al., 2019; Peh et al., 2021; Sabaté, 2003; Tan et al., 2021; Xu & Wang, 2019).

Socio-economic-Related Variables. The social/economic-related determinant data includes (a) social/environment factors (social support, culture or religious practice, life status changes like marriage or divorce); (b) economic factors (financial constraints, income); and (c) lifestyle factors (alcohol and drug use) (Bright & Stanton, 2018; Mohamed & Elamin, 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Xu & Wang, 2019).

Condition-Related Variables. The condition-related determinant variables include (a) disease control related conditions (risk factors that may increase medication non-adherence); (b) disease characteristics (time since diagnosis, stage of cancer, lymph node

involvements) and tumor characteristics (site, stage, histology, and grade) ; and (c) co-morbidities (coexisting condition with breast cancer) (Bosco-Levy et al., 2016; Farias et al., 2018b; Hagen et al., 2019; Halli-Tierney et al., 2019; Tan et al., 2021; Ma et al., 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Wulaningsih et al., 2018; Yussof et al., 2022).

Therapy-Related Variables. The therapy-related factor data included (a) medication effect (side effects); and (b) medication regimen (polypharmarcy, types and doses of medications, duration of medications) (Adidja et al., 2019; Chew et al., 2009; Dashputre et al., 2020; Mathes et al., 2014a, Molnar et al., 2016; Murphy et al., 2012; Sabaté, 2003; Yussof et al., 2022).

Health Care Team/ System-Related Variables. This determinant was described as (a) healthcare professional characteristics (prescribing practice, number of providers seen, and the historical amount of patient sharing among providers); and (b) healthcare system characteristics (coinsurance, deductible, copayment amount, total payment amount, changed charges due to healthcare errors such as wrong procedure code or invalid date of services) (Bosco-Levy et al., 2016; Guedes et al., 2017; Ma et al., 2020; Moon et al., 2017; Lambert - Côté et al., 2020; Lin et al., 2017; Peh et al., 2021; Paranjpe et al., 2019; Sabaté, 2003; Trabulsi et al., 2014).

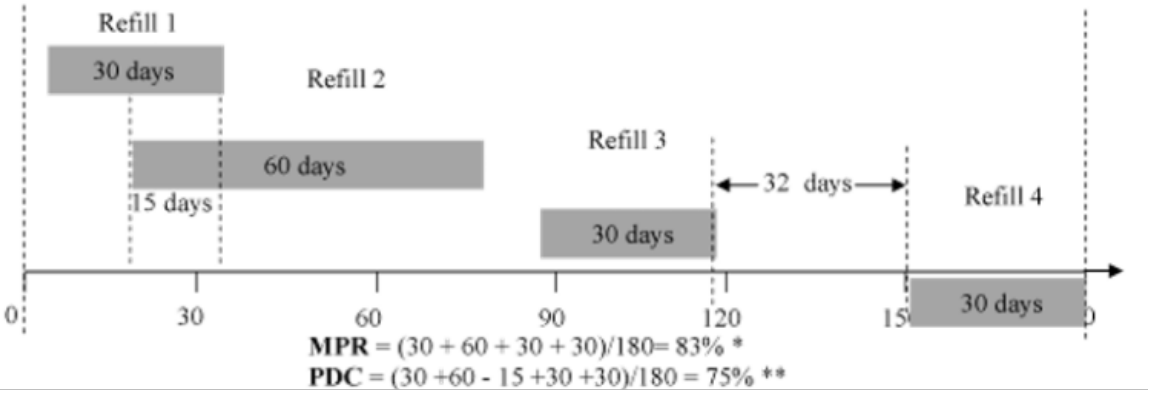
Outcome Variable: OET Non-Adherence

The primary outcome variable is OET-NA rates, which can be calculated by considering the proportion of days covered (PDC) (Davies et al., 2013). I used the "Part D Event (PDE)- with Drug Characteristics File appended" file to identify medication refill data. The PDC is the number of days covered by a prescription drug divided by the total number of days in an observation window (Centers for Medicare and Medicaid Services, 2014). I

divided the “days supply” of PDE file by the total number of days for the prescription. The PDC method was calculated in similar ways, but I deduct overlapped refill days for the PDC as shown in Figure 1. These overlapped days can be calculated by the “date of service of PDE” data. A patient with OET-NA is identified based on the PDC data using the common cut-point of <80% (non-adherent) versus ≥80% (adherent) (Chapman et al., 2008; Choudhry et al., 2008).

Figure 3.1

MPR and PDC calculation example



Procedures

I did not need to obtain informed consent since this was secondary data analysis of HIPPA compliant datasets. Since this was an IRB exempt case, the IRB cleared us to proceed. After retrieving the SEER-Medicare dataset, the medical informatic expert, Dr. Provance supported the use of a three-step process involving (a) understanding the context of SEER-Medicare data; (b) extracting data while maintaining data structures; and (c) defining data parameters (Cole et al., 2016). Next, I worked on reviewing raw data to parse that into MongoDB, which is the program that allows me to organize big datasets. I chose MongoDB

since it is a not structured query language (NoSQL) system, which provides a more flexible structure, especially when working with big data analysis that contains messy and potentially missing data (Ali et al., 2019). For instance, a field can be coded as a number, as a string, or as missing for different patients.

I extracted patient information from the Medicare Part D Event and Drug Characteristics (PDESAF) database and linked these patients' individual information to other databases such as the SEER_CANCER database, the MBSF_OTH_CC MBSF Other Chronic Condition (MBSF_OTH_CC) database, the MBSF Chronic Condition database (MBSF_ CC), the Medicare Part D Medication Therapy (PDEMTM) database, and the National Claim History (NCH) database.

The study samples were collected consecutively from the SEER-Medicare database. I extracted all available data from these databases and then identified any recurring patient identification (ID) numbers across the collective data. For example, I combined and compared data from the PDESAF and SEER-Cancer databases to compile both prescription and demographic information on each patient. Then I organized clinical characteristics and multi-level determinants from other three databases. Cancer files, Medicare Part D event files, Medicare enrollment files, and carrier claim files were used to identify these variables (Please see Table 3.1). The extracted and organized data were analyzed within the context of the research questions. Table 3.2. shows the details of possible variable codes in SEER-Medicare database for the complicated multi-level determinants. Tables 3.3, 3.4, 3.5, 3.6, and 3.7. demonstrate the code that is used for our analysis. Duplicated patient information found in the databases was considered to be one last entry per data analyst, Dr. Provance's recommendation.

A data dictionary is available in Appendix B. After reviewing all eligible samples and checking the linkage on each database, most factors being studied had clear names and values directly tied to a single variable in the data. However, comorbidity factors (Table 3.5) were retrieved from four values from the MBSF Other CC and MBSF CC databases. These four values separated the patients not only by whether or not they had a comorbidity condition, but also whether or not they had succeeded in meeting the financial criteria for a insurance claim regarding that condition. Since I was concerned with medical criteria (i.e., having diabetes) for comorbidities rather than financial criteria (i.e., fee for services cannot be provided), I reorganized this data into two value sets: patients with comorbidities and patients without.

After I retrieved the information on all variables from the different databases for analyzing five different multi-level systems, I worked on a binary logistic regression analysis for each set of factors. Next, I worked on post-hoc analysis to see the trends among all of the important factors from the five different multi-level systems.

Table 3.1.

Variables of Interest

Variables	Detailed Variables	SEER-Medicare Files
Patient-related Variables (Finitsis et al., 2019; Lambert et al., 2018; Lin et al., 2017; Moon et al., 2017; Paranjpe et al., 2019; Peh et al., 2021; Sabaté, 2003; Tan et al., 2021; Xu et al., 2019).	Demographic information (age at diagnosis, sex, race, ethnicity, and marital status)	Cancer file
	Tumor characteristics (e.g., site, stage, histology, and grade)	Cancer file
	Psychosocial factors * (mental illness such as dementia or depression diagnosis, antidepressant use, memory issue)	Other chronic or potentially disabling conditions file, Part D Event (PDE) file

	Behavioral factors* (Past drug management/therapy problems-adherence)	PDE file
Condition-related variables (Bosco-Levy et al., 2016; Farias et al., 2018b; Hagen et al., 2019; Tan et al., 2021; Ma et al., 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Wulaningsih et al., 2018; Yussof et al., 2022).	Disease control related conditions (risk factors that may increase medication non-adherence)	Medicare enrollment file
	Disease characteristics (time since diagnosis, stage of cancer, lymph node involvements)	Cancer File
	Co-morbidities (coexisting condition with breast cancer)	Medicare enrollment file
Therapy-related variable (Finitsis et al., 2019; Mohamed & Elamin, 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Yussof et al., 2022).	Pre-treatment options before starting OET* (chemotherapy, polypharmacy radiotherapy, surgical interventions such as mastectomy, lumpectomy)	Cancer file, PDE file
	Medication regimen (type of OET, dose, duration of treatment, switching OET)	PDE file
Socio-economic related variables (Bright & Stanton, 2018; Mohamed & Elamin, 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Xu & Wang, 2019).	Social/environment factors (social support, culture or religious practice, life status changes like marriage or divorce)	Cancer file
	Economic factors (financial constraints, income)	Cancer file
	Lifestyle factors (alcohol and drug use)	Cancer file
Health Care Team/ System- related variables (Bosco-Levy et al., 2016; Guedes et al., 2017; Ma et al., 2020; Moon et al., 2017; Lambert -Côté et al., 2020; Lin et al., 2017; Peh et al., 2021; Paranjpe et al., 2019; Sabaté, 2003; Trabulsi et al., 2014).	Healthcare professional characteristics * (prescribing practice, number of providers seen, and the historical amount of patient sharing among providers)	Carrier claims, Medicare enrollment, and PDE file
	Healthcare system characteristics* (coinsurance, deductible, copayment amount, total payment amount, changed charges due to healthcare errors such as wrong procedure code or invalid date of services)	Carrier claims

* These variables are explained more detailed in Table 3.2.

Table 3.2.

Variables of Interest with Code Examples

Variables	Files	Code name in SEER-Medicare database
Patient-related variables - Psychosocial factors	**Medicare Enrollment-** Chronic Conditions	Alzheimer's Disease and Related Disorders (ALZH, ALZH_DEMEN*)
	Part D Medication Therapy Management Enrollment File	Beneficiary Identified as Cognitively Impaired (COG_IMPAIRED LABEL)
	Medicare Enrollment- Other Chronic or Potentially Disabling Conditions Segment	Alcohol disorder (ALCO_MEDICARE*), Tobacco Use Disorders (TOBA_MEDICARE*), Overarching Opioid Use Disorder (OUD) (OUD_ANY_MEDICARE *), Anxiety disorder (ANXI_MEDICARE*), Personality disorders (PSDS_MEDICARE *), PTSD (PTRA_MEDICARE*), Schizophrenia and Other Psychotic Disorders (SCHIOT_MEDICARE*), Deafness and hearing impairment (HEARIM_MEDICARE*), Blindness and Visual Impairment (VISUAL_MEDICARE*), Intellectual Disabilities and Related Conditions (INTDIS_MEDICARE*), learning Disabilities (LEADIS_MEDICARE*)
Patient-related variables -Behavioral factors (Past drug therapy problems-adherence) MacDonald et al., 2018).	Part D Medication Therapy Management Enrollment File	Number of drug therapy problem recommendations to prescribers (PRESCRIBER_INTERV_NUM), Number of drug therapy problem resolutions with prescribers (DRUG_THER_CHG_NUM)
Therapy-related variables -Pre-treatment options before starting OET (chemotherapy, radiotherapy, surgical interventions such	Cancer File	Surgery of Primary Site (RX_Summ_Scope_Reg_LN_Sur), Scope of Regional Lymph Node Surgery (RX_Summ_Scope_Reg_LN_Sur), radiation and surgical procedures given as part of first course of treatment (RX_Summ_ Surg_Rad_Seq), Radiation_recoded, Chemotherapy_recoded, systemic therapy*, Neoadjuvant therapy*, Other_cancer_directed_therapy

as mastectomy, lumpectomy)	Part D Event (PDE) file	Taxotere, Ellence, Adriamycin, Xeloda, fluorouracil, Cytoxan, Paraplatin, doxorubicin
Condition-related variables Comorbidities (coexisting condition with breast cancer)	**Medicare Enrollment**-Chronic Conditions	Acute Myocardial Infarction (AMI*), Anemia (ANEMIA*), Asthma (ASTHMA*), Atrial Fibrillation (ATRIAL_FIB*), Heart Failure (CHF*), Chronic Kidney Disease (CHRONICKIDNEY*), Chronic Obstructive Pulmonary Disease (COPD*), Diabetes (DIABETES*), Hyperlipidemia (HYPERL*), Hypertension (HYPERT*), Hypothyroidism (HYPOT*), Ischemic heart disease (ISCHEMICHEART*), Osteoporosis (OSTEOPOROSIS*), Rheumatoid Arthritis (RA_OA*), Stroke / Transient Ischemic Attack (STROKE_TIA*)
	Medicare Enrollment-Other Chronic or Potentially Disabling Conditions Segment	Viral Hepatitis (HEPVIRAL_MEDICARE*), HIV/AIDS(HIVAIDS_MEDICARE*), Liver related conditions (LIVER_MEDICARE*), Migraine and other Chronic Headache (MIGRAINE__MEDICARE*), Peripheral Vascular Disease (PVD_MEDICARE*), Sickle Cell Disease (SCD_MEDICARE*)
Condition-related variables -Disease control related conditions (risk factors that may increase medication non-adherence)	**Medicare Enrollment**-Chronic Conditions	Previous colorectal cancer diagnosis date (CANCER_COLORECTAL_ EVER), Endometrial Cancer diagnosis date (CANCER_ ENDOMETRIAL_EVER), Cataract diagnosis date (CATARACT_EVER), Glaucoma diagnosis date (GLAUCOMA_EVER), Depression (DEPRESSION*), Hip fracture history (HIP_FRACTURE_EVER)
	Other Chronic or Potentially Disabling Conditions Segment	Leukemias and Lymphomas (LEUKLYMPH_MEDICARE*), Obesity (OBESITY_MEDICARE*), Pressure Ulcers and Chronic Ulcers (ULCERS_MEDICARE*)
	Cancer File	Mobility Impairments (MOBI_MEDICARE*), Spinal Cord Injury (SPIINJ_MEDICARE*), metastasis (REGIONAL NODES POSITIVE, METS AT DX*)
Condition-related Variables **-** Polypharmacy	NCH (Carrier Claims)	Claim Related Condition Code (CLM_RLT_COND_CD) i.e., 22 = Patient on multiple drug regimen — a patient who is receiving

		multiple intravenous drugs while on home IV therapy
Healthcare professional characteristics (prescribing practice, and the historical amount of patient sharing among providers)	Part D Prescriber Characteristics and Medicare Data on Provider Practice and Specialty (MD-PPAS) file	National provider identifier (NPI)
	Medicare Data on Provider Practice and Specialty (MD-PPAS) file	Provider Specialty (spec_broad, spec_prim_1 spec_prim_1_name spec_prim_2 spec_prim_2_name spec_source spec_source_hosp)
	NCH (Carrier Claims)	REV_CNTR_1ST_ANSI_CD , REV_CNTR_2ND_ANSI_CD, REV_CNTR_3RD_ANSI_CD, REV_CNTR_4TH_ANSI_CD • B17 = Claim/service adjusted because this service was not prescribed by a physician, not prescribed prior to delivery, the prescription is incomplete, or the prescription is not current • B19 = Claim/service adjusted because of the finding of a Review Organization. INACTIVE • B20 = Charges adjusted because procedure/service was partially or fully furnished by another provider • B21 = The charges were reduced because the service/care was partially furnished by another physician. INACTIVE • B23 = Claim/service denied because this provider has failed an aspect of a proficiency testing program

Healthcare system characteristics (coinsurance, deductible, copayment amount, total payment amount, changed charges due to healthcare errors such as wrong procedure code or invalid date of services)	NCH (Carrier Claims)	**CLM_VAL_CD (Claim Value Code)** • 25 = Offset to the Patient Payment Amount (Prescription Drugs) — prescription drugs paid for out of a long-term care facility resident/patient's fund in the billing period submitted (Statement Covers Period) • 35 = Offset to the Patient Payment Amount (Health Insurance Premiums) — Other medical services paid out of a long-term care facility resident/ patient's funds in the billing period submitted • 70 = Interest amount — (providers do not report this.) Report the amount applied to this bill • A1 = Deductible Payer A — the amount assumed by the provider to be applied to the patient's deductible amount to the involving the indicated payer. (eff. 10/1993) — Prior value 0 • A2 = Coinsurance Payer A — the amount assumed by the provider to be applied to the patient's Part B coinsurance amount involving the indicated payer • A7 = Copayment A — the amount assumed by the provider to be applied toward the patient's copayment amount involving the indicated payer **REV_CNTR_1ST_ANSI_CD , REV_CNTR_2ND_ANSI_CD, REV_CNTR_3RD_ANSI_CD, REV_CNTR_4TH_ANSI_CD** • PR = Patient Responsibility — this group should be used when the adjustment represents an amount that should be billed to the patient or insured. This group would typically be used for deductible and copay adjustments • 2 = Coinsurance Amount • 3 = Co-pay Amount • 5 = The procedure code/bill type is inconsistent with the place of service • 126 = Deductible — major Medical • 127 = Coinsurance — major Medical • B18 = Claim/service denied because this procedure code/modifier was invalid on the date of service or claim submission
Healthcare system	Medicare Data on Provider Practice	Geographic location (state, cbsa_type), Utilization summary measures (npi_srvc_lines,

characteristics (location of healthcare, utilizing or visiting healthcare facility)	and Specialty (MD-PPAS) file	npi_allowed_amt npi_unq_benes), Plan of service that is delivered in office, outpatient department, hospital, patient's residence (Pos_office, pos_opd, pos_inpat, post _ER, pos_resid),

Table 3.3.

Patient-Related Variable Codes

	Database and Codes
White	SEER_CANCER RACE_RECODE_W_B_AI_API 1
Black	SEER_CANCER RACE_RECODE_W_B_AI_API 2
American Indian/Alaska Native	SEER_CANCER RACE_RECODE_W_B_AI_API 3
Asian or Pacific Islander	SEER_CANCER RACE_RECODE_W_B_AI_API 4
Anxiety (Y)	MBSF_OTH_CC ANXI_MEDICARE 1,3
Anxiety (N)	MBSF_OTH_CC ANXI_MEDICARE 2,4
Depression (Y)	MBSF_OTH_CC DEPSN_MEDICARE 1,3
Depression (N)	MBSF_OTH_CC DEPSN_MEDICARE 2,4
Alzheimer's (dementia) Disease (Y)	MBSF_CC ALZH_DEMEN 1,3
Alzheimer's (dementia) Disease (N)	MBSF_CC ALZH_DEMEN 2,4
Brain Damage (Y)	MBSF_OTH_CC BRAINJ_MEDICARE 1,3
Brain Damage (N)	MBSF_OTH_CC BRAINJ_MEDICARE 2,4
Intellectual Disabilities (Y)	MBSF_OTH_CC INTDIS_MEDICARE 1,3
Intellectual Disabilities (N)	MBSF_OTH_CC INTDIS_MEDICARE 2,4
Learning Disabilities (Y)	MBSF_OTH_CC LEADIS_MEDICARE 1,3
Learning Disabilities (N)	MBSF_OTH_CC LEADIS_MEDICARE 2,4

ADHD and Other Conduct Disorder (Y)	MBSF_OTH_CC ACP_MEDICARE 1,3
ADHD and Other Conduct Disorder (N)	MBSF_OTH_CC ACP_MEDICARE 2,4
Bipolar Disorder (Y)	MBSF_OTH_CC BIPL_MEDICARE 1,3
Bipolar Disorder (N)	MBSF_OTH_CC BIPL_MEDICARE 2,4
Personality Disorders (Y)	MBSF_OTH_CC PSDS_MEDICARE 1,3
Personality Disorders (N)	MBSF_OTH_CC PSDS_MEDICARE 2,4
PTSD (Y)	MBSF_OTH_CC PTRA_MEDICARE 1,3
PTSD (N)	MBSF_OTH_CC PTRA_MEDICARE 2,4
Schizophrenia and Related Conditions (Y)	MBSF_OTH_CC SCHIOT_MEDICARE 1,3
Schizophrenia and Related Conditions (N)	MBSF_OTH_CC SCHIOT_MEDICARE 2,4
Hearing Impairment (Y)	MBSF_OTH_CC HEARIM_MEDICARE 1,3
Hearing Impairment (N)	MBSF_OTH_CC HEARIM_MEDICARE 2,4
Mobility impairment (Y)	MBSF_OTH_CC MOBIMP_MEDICARE 1,3
Mobility impairment (N)	MBSF_OTH_CC MOBIMP_MEDICARE 2,4
Visual impairment (Y)	MBSF_OTH_CC VISUAL_MEDICARE 1,3
Visual impairment (N)	MBSF_OTH_CC VISUAL_MEDICARE 2,4

Table 3.4.

Socioeconomic-Related Variable Codes

	Database and Codes
Single (never married)	SEER_CANCER MARITAL_STATUS_AT_DIAGNOSIS 1
Married	SEER_CANCER MARITAL_STATUS_AT_DIAGNOSIS 2
Separated	SEER_CANCER MARITAL_STATUS_AT_DIAGNOSIS 3

Divorced	SEER_CANCER MARITAL_STATUS_AT_DIAGNOSIS 4
Widowed	SEER_CANCER MARITAL_STATUS_AT_DIAGNOSIS 5
Alcohol use (Y)	MBSF_OTH_CC ALCO_MEDICARE 1,3
Alcohol use (N)	MBSF_OTH_CC ALCO_MEDICARE 2,4
Drug use (Y)	MBSF_OTH_CC DRUG_MEDICARE 1,3
Drug use (N)	MBSF_OTH_CC DRUG_MEDICARE 2,4
Opioid drug use (Y)	MBSF_OTH_CC OUD_ANY_MEDICARE 1,3
Opioid drug use (N)	MBSF_OTH_CC OUD_ANY_MEDICARE 2,4
Opioid use for MAT[a] (Y)	MBSF_OTH_CC OUD_MAT_MEDICARE 1,3
Opioid use for MAT[a] (N)	MBSF_OTH_CC OUD_MAT_MEDICARE 2,4
Tobacco use (Y)	MBSF_OTH_CC TOBA_MEDICARE 1,3
Tobacco use (N)	MBSF_OTH_CC TOBA_MEDICARE 2,4
Metro area	SEER_CANCER RURAL_URBAN_CONTINUUM_CODE_2003 01,02,03
Urban area	SEER_CANCER RURAL_URBAN_CONTINUUM_CODE_2003 04,05,06,07
Completely Rural area	SEER_CANCER RURAL_URBAN_CONTINUUM_CODE_2003 08,09

[a]MAT = Medication-Assisted Treatment

Table 3.5.

Therapy-Related Variable Codes

	Database and Codes
OET medication switched (Y)	PDESAF_pdc_mpr_results MEDS_SWITCHED True
OET medication switched (N)	PDESAF_pdc_mpr_results MEDS_SWITCHED False
No systemic chemo and/or surgical therapy	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 0
Systemic therapy before surgery	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 2
Systemic therapy after surgery	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 3
Systemic therapy both before and after surgery	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 4
Intraoperative systemic therapy	SEER_CANCER

	RX_SUMM_SYSTEMIC_SURG_SEQ 5
Intraoperative systemic therapy with other therapy	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 6
Surgery both before and after systemic therapy	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 7
Sequence unknown, but both surgery and systemic therapy are given	SEER_CANCER RX_SUMM_SYSTEMIC_SURG_SEQ 9
No radiation and /or surgery	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 0
Radiation before surgery	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 2
Radiation after surgery	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 3
Radiation both before and after surgery	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 4
Intraoperative radiation	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 5
Intraoperative radiation with other radiation given	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 6
Surgery both before and after radiation	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 7
Sequence unknown, but both surgery and radiation were given	SEER_CANCER RX_SUMM_SURG_RAD_SEQ 9
No Drug Therapy problem	PDEMTM DRUG_THER_CHG_NUM 0
1st Drug Therapy problem	PDEMTM DRUG_THER_CHG_NUM 1
2nd Drug Therapy problem	PDEMTM DRUG_THER_CHG_NUM 2
3rd Drug Therapy problem	PDEMTM DRUG_THER_CHG_NUM 3
4th Drug Therapy problem	PDEMTM DRUG_THER_CHG_NUM 4

Table 3.6.

Condition- Related Variable Codes

	Database and Codes
Stage 0	SEER_CANCER COMBINED_SUMMARY_STAGE_2004 0
Stage I	SEER_CANCER COMBINED_SUMMARY_STAGE_2004 1
Stage II	SEER_CANCER COMBINED_SUMMARY_STAGE_2004 2
Stage III	SEER_CANCER COMBINED_SUMMARY_STAGE_2004 7

Stage IV	SEER_CANCER COMBINED_SUMMARY_STAGE_2004 9
AMI (Y)	MBSF_CC AMI 1,3
AMI (N)	MBSF_CC AMI 2,4
Anemia (Y)	MBSF_CC ANEMIA 1,3
Anemia (N)	MBSF_CC ANEMIA 2,4
Asthma (Y)	MBSF_CC ASTHMA 1,3
Asthma (N)	MBSF_CC ASTHMA 2,4
CHF (Y)	MBSF_CC CHF 1,3
CHF (N)	MBSF_CC CHF 2,4
COPD (Y)	MBSF_CC COPD 1,3
COPD (N)	MBSF_CC COPD 2,4
CKD (Y)	MBSF_CC CHRONICKIDNEY 1,3
CKD (N)	MBSF_CC CHRONICKIDNEY 2,4
Diabetes (Y)	MBSF_CC DIABETES 1,3
Diabetes (N)	MBSF_CC DIABETES 2,4
Epilepsy (Y)	MBSF_OTH_CC EPILEP_MEDICARE 1,3
Epilepsy (N)	MBSF_OTH_CC EPILEP_MEDICARE 2,4
Fibromyalgia Chronic Pain and Fatigue (Y)	MBSF_OTH_CC FIBRO_MEDICARE 1,3
Fibromyalgia Chronic Pain and Fatigue (N)	MBSF_OTH_CC FIBRO_MEDICARE 2,4
Hepatitis (Viral) (Y)	MBSF_OTH_CC HEPVIRAL_MEDICARE 1,3
Hepatitis (Viral) (N)	MBSF_OTH_CC HEPVIRAL_MEDICARE 2,4
Hip Fracture (Y)	MBSF_CC HIP_FRACTURE 1,3
Hip Fracture (N)	MBSF_CC HIP_FRACTURE 2,4
HIV/AIDS (Y)	MBSF_OTH_CC HIVAIDS_MEDICARE 1,3
HIV/AIDS (N)	MBSF_OTH_CC HIVAIDS_MEDICARE 2,4
Hyperlipidemia (Y)	MBSF_CC HYPERL 1,3
Hyperlipidemia (N)	MBSF_CC HYPERL 2,4
Hypertension (Y)	MBSF_CC HYPERT 1,3
Hypertension (N)	MBSF_CC HYPERT 2,4
Hypothyroid (Y)	MBSF_CC HYPOTH 1,3
Hypothyroid (N)	MBSF_CC HYPOTH 2,4

Leukemia and lymphomas (Y)	MBSF_OTH_CC LEUKLYMPH_MEDICARE 1,3
Leukemia and lymphomas (N)	MBSF_OTH_CC LEUKLYMPH_MEDICARE 2,4
Liver Diseases (Y)	MBSF_OTH_CC LIVER_MEDICARE 1,3
Liver Diseases (N)	MBSF_OTH_CC LIVER_MEDICARE 2,4
Migraine and Other Chronic Headache (Y)	MBSF_OTH_CC MIGRAINE_MEDICARE 1,3
Migraine and Other Chronic Headache (N)	MBSF_OTH_CC MIGRAINE_MEDICARE 2,4
Obesity (Y)	MBSF_OTH_CC OBESITY_MEDICARE 1,3
Obesity (N)	MBSF_OTH_CC OBESITY_MEDICARE 2,4
Osteoporosis (Y)	MBSF_CC OSTEOPOROSIS 1,3
Osteoporosis (N)	MBSF_CC OSTEOPOROSIS 2,4
PVD (Y)	MBSF_OTH_CC PVD_MEDICARE 1,3
PVD (N)	MBSF_OTH_CC PVD_MEDICARE 2,4
Spinal Injury (Y)	MBSF_OTH_CC SPIINJ_MEDICARE 1,3
Spinal Injury (N)	MBSF_OTH_CC SPIINJ_MEDICARE 2,4
Ulcers (Y)	MBSF_OTH_CC ULCERS_MEDICARE 1,3
Ulcers (N)	MBSF_OTH_CC ULCERS_MEDICARE 2,4

Table 3.7

Health Care Team/System-Related Factors

	Database and Codes
CMR provider-Physician	PDEMTM CMR_PROVIDER 01
CMR provider-Registered Nurse	PDEMTM CMR_PROVIDER 02
CMR provider-Licensed practical nurse	PDEMTM CMR_PROVIDER 03
CMR provider-Nurse practitioner	PDEMTM CMR_PROVIDER 04
CMR provider-Pharmacist	PDEMTM CMR_PROVIDER 05
Group Practitioners in Clinic	NCH_LINE CARR_LINE_PRVDR_TYPE_CD 0
Solo Practitioners	NCH_LINE CARR_LINE_PRVDR_TYPE_CD 1
Institution providers (share patients)	NCH_LINE CARR_LINE_PRVDR_TYPE_CD 3
Coinsurance amount $0-20	NCH_LINE LINE_COINSRNC_AMT 0

Coinsurance amount $20-40	NCH_LINE LINE_COINSRNC_AMT 1
Coinsurance amount $40-60	NCH_LINE LINE_COINSRNC_AMT 2
Coinsurance amount $60-80	NCH_LINE LINE_COINSRNC_AMT 3
Coinsurance amount $80-100	NCH_LINE LINE_COINSRNC_AMT 4
Health care service subject to deductible (Y)	NCH_LINE LINE_SERVICE_DEDUCTIBLE 1
Health care service subject to deductible (N)	NCH_LINE LINE_SERVICE_DEDUCTIBLE 0

Data Analysis

Data was be managed using Python (version 3.11.4) for the secondary analysis to find OET-NA and multi-level determinants. The alpha level for this study is 0.05. Analysis was performed under the supervision of a biostatistician, Dr. Chestnut. Descriptive statistics was utilized to interpret demographic data, which includes patient age groups (ordinal level), race (ordinal level), and marital status (ordinal level). The descriptive statistics of ordinal level data was including the total number and its percentage, and the ratio level data had mean, standard deviation, and range (Polit & Beck, 2020).

Research Question #1: What is the rate of OET-NA in women with breast cancer?

Analysis Plan: The OET- NA will be calculated as the percentage of NA rates to OET among women with breast cancer who are taking OET. This data will be collected as ratio level and arranged in a descriptive statistical analysis table with demographic data.

Research Question #2: What are the multi-level determinants influencing OET-NA in women with breast cancer?

Analysis Plan: The OET-NA is the main outcome variable and nominal level of data. The univariate and multivariate binary logistic regression statistical test will be computed to assess the relationship between multi-level determinants and OET-NA with odds ratio at a significance level of 0.05.

The data analysis was conducted on each multi-level factors derived from the WHO's FDM and the correlation analysis was computed to identify the trends of medication-NA factor among older female breast cancer patients in the U.S.

CHAPTER 4

RESULTS

This chapter includes the results of the RESILIENT study, a descriptive, correlational investigation of the rate and correlation of OET-NA in women with breast cancer. This chapter will be presented in three sections. The first section is a summary of the samples using descriptive statistics, the second section seeks to answer the first research question by identifying OET-NA rates, and the final section seeks to answer the second research question by finding determinants of OET-NA.

Characteristics of the Samples

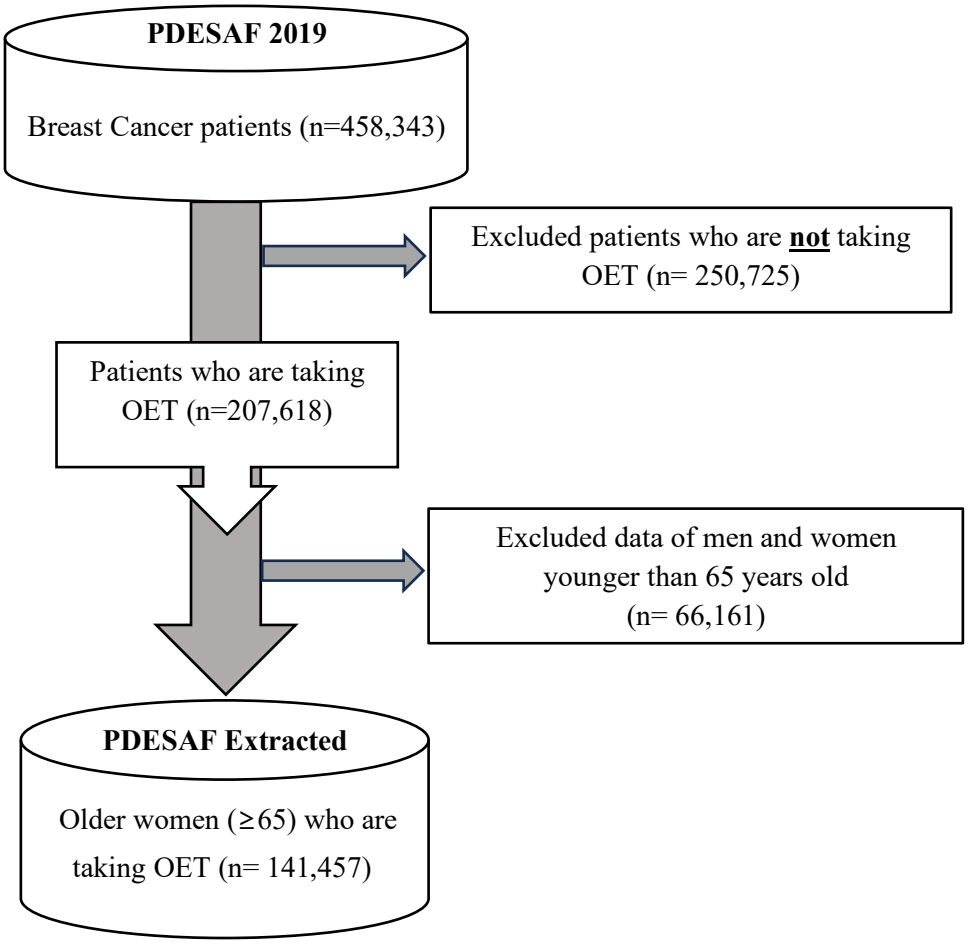
A total of six databases were utilized to conduct this study: (a) the Master Beneficiary Summary File (MBSF) chronic condition database, (b) the MBSF other chronic condition database, (c) the National Claims History (NCH) database, (d) the Medicare Part D Medication Therapy (PDEMTM) database, (e) the Medicare Part D Event and Drug Characteristics (PDESAF) database, and (f) the SEER Cancer database (SEER, 2022a). Due to the disconnectedness of these databases, the Mongo database was used in conjunction with C++ and Python to link and organize all of the data. This allowed the investigator to efficiently review all eligible samples, check each database's lineage, and subsequently answer research question one and two. Research question number one focused on ten years of OET studies to calculate OET-NA rates from 2010 to 2019 to see the trends of OET-NA. Research question number two identified OET-NA determinants on breast cancer patients from 2019 data, which is the most updated available from the SEER Medicare (released early 2023).

Study Samples

The study samples were collected from the 2019 SEER-Medicare database, using this study's inclusion criteria, to collect pertinent medication adherence data. The sub-sampling process is outlined in Figure 4.1.

Figure 4.1.

Sample Extraction Diagram

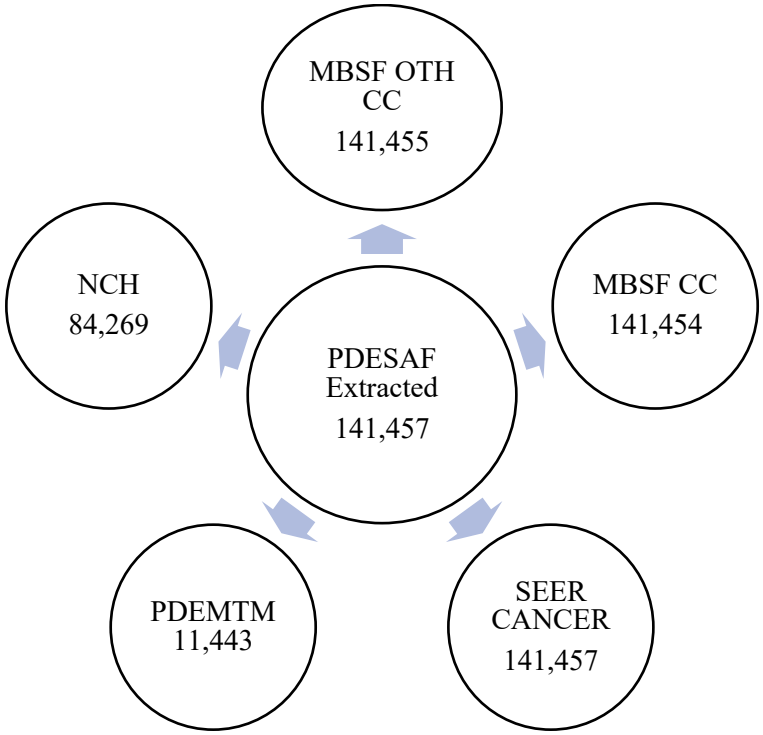


The total number of breast cancer patients in the "PDESAF 2019" database was 458,343. After excluding patients who were not taking OET medications, the remaining patient count was 207,618 (Figure 4.1). After applying the study's inclusion criteria, the data

was filtered down to 141,457 older women with breast cancer (≥65) in OET therapy. These sub-subsampled patients were copied to a new database, referred to as "PDESAF Extracted". The patient IDs from this new database, along with their OET-NA status (i.e., adherent as PDC≥80, non-adherent as PDC <80), were selected as the dependent variable of this study.

Figure 4.2.

Relevant Patient Count in Linked Databases



After reviewing all 141,457 patient IDs for the dependent variable, patient information was matched from the "PDESAF Extracted" database to the other databases by referencing the patient IDs to find matches. Figure 4.2 shows the total common patient count found between "PDESAF Extracted" and each of the five databases used in this study. I found information for 141,455 patients in the MBSF OTH CC database which had

corresponding patient IDs in our dependent variable PDESAF Extracted database (n=141,457), meaning two patients had no information in the MBSF OTH CC database (Figure 4.2.). Each database had matching patient IDs, leading to 141,454 retrieved patients in the MBSF CC database, 141,454 in the SEER CANCER database, 11,443 in the PDEMTM database and 84,269 in the NCH database, respectively.

As might be expected with pulling data from so many databases, there was a percentage of data missing. Most of the information was complete; however, two major categories had roughly 60% completion. Marital status, for example, was 42% unknown and therapy combination was 39% unknown. Other demographic items had less than 0.73% unknown or missing data (see Table 4.3). This missing data can be counted as either being reported unknown if an unknown variable value was selected by or on behalf of the patient or the relevant field for a patient had no value at all and was left empty in the database. Specifically, an unknown variable value is identified for a particular field in the data dictionary. For instance, the field "RACE RECODE" in the SEER CANCER database has values from categorically ethnic values from 1 to 4, a value of 9 indicates a patient's ethnicity is unknown as described in the data dictionary.

Fortunately, the logistic regression tool automatically checked for data completeness and thus removes all the missing data before the analysis. So, while I started with a very large sample size overall, I may have had a smaller sample size for analysis for a particular factor depending on the amount of missing data for the fields selected. To avoid ambiguous inferences, I did not include any missing data. In my odds ratio plots, I included sample size numbers for each analysis based on the actual data count used.

Demographics of Study Samples

Retrieved demographic data is presented in descriptive statistics (Table 4.1.) to portray the characteristics of all eligible samples. All demographic items including ethnicity, sex, age, marital status at diagnosis, residence type, and year of diagnosis were collected from the SEER Cancer database.

Table 4.1

Demographics of 2019 Breast Cancer Patients Taking OET Medications (N= 141,457)

Demographics	Count	Percentage (%)
Race		
White	117,873	83.33
Black	13,852	9.79
American Indian/Alaska Native	459	0.32
Asian or Pacific Islander	8,238	5.82
Unknown	1,035	0.73
Age		
Mean Age	73.16	
(Min/Max/σ)	(65/99/6.42)	
65-74	92,044	65.07
75-84	40,338	28.52
85-99	9,046	6.39
Unknown	29	0.02
Cancer Stage		
Stage I	92,450	65.36
Stage II	29,971	21.19
Stage III	4,909	3.47
Stage IV	2,416	1.71
Unknown	11,711	8.28
Marital Status at Diagnosis		
Single (never married)	9,104	6.44
Married (including common law)	42,354	29.94
Separated	572	0.4
Divorced	9,923	7.01
Widowed	19,487	13.78
Unknown	60,017	42.43

Year of Diagnosis for 2019 Cancer Patients		
2010	2,616	1.85
2011	3,839	2.71
2012	5,101	3.61
2013	8,137	5.75
2014	14,838	10.49
2015	17,790	12.58
2016	20,008	14.14
2017	22,567	14.39
2018	26,205	18.53
2019	20,356	14.39
Unknown	0	0
Rural Urban Status		
Metro area (more than 250,000 populations)	125,289	88.57
Urban area (more than 2,500 populations)	14,668	10.37
Rural area (less than 2,500 populations)	1,495	1.06
Unknown	0	0.00
Switch Medication Status		
Prescribed medication was changed	7,607	5.38
Prescribed medication was not changed	133,850	94.62
OET Medication		
Anastrozole	78,256	55.32
Exmestane	9,663	6.83
Letrozole	33,864	23.92
Tamoxifen	19,674	13.91
Systemic and Surgical Therapy		
No systemic therapy[a] and/or surgical therapy	21,613	15.28
Systemic therapy[a] before surgery	1,870	1.32
Systemic therapy[a] after surgery	59,050	41.74
Systemic therapy[a] both before and after surgery	2,605	1.84
Intraoperative systemic therapy[a]	25	0.02
Intraoperative systemic therapy[a] with other therapy	36	0.03
Surgery both before and after systemic therapy[a]	599	0.42
Sequence unknown, but both surgery and systemic therapy are given	47	0.03
Unknown	55,612	39.31
Radiation and Surgical Therapy		
No radiation and/ or surgery	42,397	29.97
Radiation before surgery	145	0.10
Radiation after surgery	42,153	29.80

Radiation both before and after surgery	85	0.06
Intraoperative radiation	832	0.59
Intraoperative radiation with other radiation given	184	0.13
Surgery both before and after radiation	14	0.01
Sequence unknown, but both surgery and radiation were given	35	0.02
Unknown	55612	39.31

[a]Systemic therapy is systemic chemotherapy that is affected whole body systems with medications such as cytotoxic medications to kill the cancer cells.

Ethnicity, sex, age, marital status at diagnosis, residence type, and year of diagnosis are defined as follows.

Ethnicity

Race data identifies patient's ethnicity into five major categories: White, Black, American Indian/Alaska Native, and Asian/Pacific Islander, and other.

Sex

This data item identifies the sex of the patient at diagnosis: female or male.

Age

Age represents the age of the patient at the time of cancer diagnosis. Age is categorized into the following categories: 65-74, 75-84, 85-99, and unknown.

Marital Status at Diagnosis

This item identifies the patient's marital status at time of diagnosis as one of six options: single (never married), married (including common law), separated, divorced, widowed, and unmarried or domestic partner (same sex or opposite sex or unregistered).

Stage of Cancer

This item identifies the patient's cancer stage, which was discussed in Chapter 2. Stage 0, carcinoma in-situ, describes the presence of abnormal cells that have not spread to nearby tissues. Stage I, the early stage, describes when the cancer has spread to other tissue

in a small area. Stage II, the localized stage, describes when tumor size ranges between 20-50 mm and there is some lymph node involvement or when a tumor is larger than 50 mm without any lymph node involvement. Stage III, the regional spread stage, described a tumor larger than 50 mm with greater lymph nodes involvement across a wider region. Finally, Stage IV, the distant spread stage, described when cancer has spread beyond the breast to other distant parts of the body.

Medications

This item includes all different types of OET medications such as anastrozole, letrozole, tamoxifen citrate, and exmestane.

Switch Medication Status

This item documents that the patient's prescriber switched the patient's OET-medication among anastrozole, letrozole, tamoxifen citrate, and exmestane. The possible value of this item is either (a) prescribed medication was changed or (b) prescribed medication was not changed.

Systemic and Surgical Therapy

This item shows the order in which systemic therapy and surgery were administered for patients who required both. This combination is often used as the initial course of treatment.

Radiation and Surgical Therapy

This item shows the order in which surgery and radiation therapies were administered for those patients who had both surgery and radiation.

Summary of the Study Samples

In 2019, 141,457 breast cancer patients were taking OET per the SEER Medicare database. The mean age of this population was 73.16 years old. Most patients were White (83.33%), married (29.94%), and living in a metropolitan area (88.57%). The vast majority were Stage I at first diagnosis (65.36%), required systemic chemotherapy after surgery (41.74%), no radiation and/or surgery (29.97%), and took AI medications such as anastrozole (55.32%), exemestane (6.83%), and letrozole (23.92%). More than 25% of patients were diagnosed between 2010 and 2014 and about 75% of patients between 2015 and 2019. These trends were similarly reported in other years of the SEER-Medicare database studies (Farias & Du, 2017; Haskins et al., 2019; Wang & Du, 2015; Yuan et al., 2020). Unfortunately, there were significant amounts of missing/unknown data in systemic-chemo, radiation, and surgical therapy (39.31%). This makes it difficult to understand the underlying reason for specific therapy-related determinants for OET-NA.

Results of Research Question 1: Identifying OET-NA Rates

Research question number one is designed to identify the rate of OET adherence in women with breast cancer.

2019 MPR and PDC Data

The MPR estimates the proportion (or percentage) of days medication was supplied during a specified time period, while the PDC estimates the number of days covered over a time interval. In this study, both the MPR and PDC data are used to calculate medication adherence (Table 4.2). The rates of OET medication adherence were 98.06% (MPR) and 93.65% (PDC). The rates of OET-NA were 1.94% (MPR) and 6.35% (PDC). The MPR OET-NA rates were lower than the PDC method as it accounted for extra dates. The lowest

OET-NA rate was 6.09% (PDC) for anastrozole, which indicates this is the OET medication patients were most likely to be adherent to. However, other OET medications have similar ranges of NA, from 6.42-7.58%. OET-NA was grouped into categories based on the PDC data using the common cut-point of <80% (non-adherent); while adherent groups showed PDC rates ≥80% (adherent) (Chapman et al., 2008; Choudhry et al., 2008). Again, anastrozole was the smallest (8%) OET-NA group, and the biggest OET-NA group was patients taking exmestane (6.83%) (Table 4.3).

Table 4.2

The Rate of OET Medication Adherence and OET-NA Rates in 2019

Medication	Percentage (%)	MPR (%)	MPR Min/Max/ SD (%)	PDC (%)	PDC Min/Max/ SD (%)	MPR OET-NA (%)	PDC OET-NA (%)
Entire OET	100	98.06	10.73/823/ 13.11	93.65	10.73/100/ 9.59	1.94	6.35
Anastrozole	55.32	97.97	14.34/823/12. 20	93.91	11.53/100/ 9.15	2.03	6.09
Exmestane	6.83	98.67	10.73/407/ 17.07	92.42	10.73/100/ 11.00	1.33	7.58
Letrozole	23.94	98.13	15.34/387/ 13.10	93.58	15.34/100/ 13.10	1.87	6.42
Tamoxifen	13.91	98.03	12.94/495 / 14.32	93.33	12.94/100/ 10.15	1.97	6.67

Table 4.3

OET Medication Adherence in 2019

Medication	Counts (%)	OET adherent counts (%)	OET-NA counts (%)

Anastrozole	78,256 (55.32%)	73,490 (93.91%)	4,766 (6.09%)
Exmestane	9,663 (6.83%)	8,931 (92.42 %)	732 (7.58%)
Letrozole	33,864 (23.92%)	31,690 (93.58%)	2,174 (6.42%)
Tamoxifen	19,674 (13.91%)	18,362 (93.33%)	1,312 (6.67%)

The Rate of OET-NA over Ten years

I extended the OET-NA rates from 2010 to 2019 to see the trends of rates, which will enhance understanding of 2019 OET-NA rates data. The average OET adherence rate over ten years was 92.85% (PDC) and 97.22% (MPR). The average OET-NA rate was 7.15% (PDC) and 2.78% (MPR). Each year data and its sample size are available in Table 4.4.

Table 4.4.

Descriptive Statistics of OET Medication Adherence and NA Rates 2010- 2019

Year	MPR (%)	MPR Min/Max/ SD (%)	PDC (%)	PDC Min/Max/ SD (%)	MPR OET-NA (%)	PDC OET-NA (%)	Counts
2010	97.31	12.60/457.14/14.85	93.39	12.60/100/ 11.23	2.69	6.61	16,323
2011	96.96	12.60/2325/ 19.10	92.50	12.60/100/ 11.20	3.04	7.5	35,930
2012	96.90	8.38/766/14. 39	92.46	8.38/100/ 10.82	3.1	7.54	58,723
2013	96.95	0/850/14.04	92.47	0.00/100/ 10.5	3.05	7.53	88,851
2014	96.93	0.00/1000/ 14.47	92.40	0.00/100/ 10.6	3.07	7.6	115,409
2015	96.93	3.73/3100/ 17.94	92.53	3.73/100/ 10.48	3.07	7.47	142,355
2016	97.07	9.30/2400/ 14.91	92.71	9.30/100/ 10.46	2.93	7.29	161,862
2017	97.34	12.83/1385/ 13.68	93.01	12.83/100/ 10.14	2.66	6.99	178,272

2018	97.72	1.64/1100/ 13.57	93.34	1.64/100/ 9.94	2.28	6.66	158,521
2019	98.06	10.73/823/ 13.11	93.65	10.73/100/ 9.59	1.94	6.35	141,457

Results of Research Question 2: Finding Determinants of OET-NA

The second research question was designed to identify the multi-level determinants influencing OET-NA in older women with breast cancer. Determinants were identified by using odds ratio analysis. To calculate the odds ratio, the OET-NA group (PDC <80%) and the OET adherent group (PDC ≥80%) were divided by either having the condition (True for A Factor) and not having condition (False for A Factor) (Table 4.5).

Table 4.5.

Odds Ratio Example

Patient counts	True for A Factor	False for A Factor
OET-NA group	237	13,273
OET adherent group	2,152	144,433

To interpretate an odds ratio, its value must be compared to 1: (a) if the odds ratio is greater than 1, the odds of the chosen factor (True for A Factor) were more likely to occur in the OET-NA group (positive association between the OET-NA and chosen factor); (b) if the odds ratio is less than 1, the odds of the chosen factor (True for A Factor) were less likely to occur in the OET-NA group (negative association between the OET-NA and chosen factor); and (c) if the odds ratio is equal to 1, the odds of NA were the same with or without the chosen factor (True for A Factor) to occur (no association between the OET-NA and chosen factor). For example, when the chosen factor is diabetes and the odds ratio is greater than 1, it

suggests that the odds of having diabetes were more likely to occur in the OET-NA group. This can be also interpreted that having diabetes is a positive determinant or risk factor for OET-NA.

Patient-Related Factors

Among patient-related factors described in previous chapters, race/ethnicity data and psychological data were analyzed here. Multivariate binary logistic regression analysis was conducted to calculate the Adjusted OR (AOR) of the 141,457 patient samples for ethnicity in the SEER Cancer database (Table 4.6) and available samples for psychological symptoms, cognitive issues, and psychological diseases are avialable (Figure 4.2, 4.3, 4.5 and 4.6). Those with White ethnicity and no psychological conditions were selected as a reference group, due to the significant amount of data points, allowing the investigation of different patient-related factors on OET-NA. From this analysis, Black (AOR 1.51; 95% CI 1.43-1.60; $p < 0.001$) and American Indian/Alaska Native (AOR 1.42; 95% CI 1.06-1.91; $p < 0.001$) ethnic groups were identified as more likely to have OET-NA than other ethnic groups (Table 4.6). Having psychological symptoms such as anxiety (AOR 1.15; 95% CI 1.08-1.23; $p < 0.001$) and depression (AOR 1.49; 95% CI 1.39-1.59; $p < 0.001$) were identified as determinants (Table 4.7). In other words, patients with anxiety were 21% more likely to be OET-NA while patients with depression were 48% more likely to be OET-NA. Moreover, Alzheimer's disease (AOR 1.76; 95% CI 1.63-1.89; $p < 0.001$) was associated with greater OET-NA among breast cancer patients than other cognitive issues (Table 4.8). Interestingly, ADHD (AOR 1.65; 95% CI 1.17-2.32; $p < 0.001$) was the strongest determinant of OET-NA among other psychological diseases (Table 4.9). All other psychological diseases were positively associated with OET-NA. Also, mobility impairment (AOR 1.61; 95% CI 1.37-

1.88; p <0.001) was identified as a determinant of OET-NA, but hearing and visual sensory impairments were not statistically significant (Table 4.10).

Table 4.6.

Patient-Related: Ethnicity Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
White	0.8	0.77	0.84	<0.001	-	-	-	-
Black	1.52	1.44	1.61	<0.001	1.51	1.43	1.6	<0.001
American Indian/Alaska Native	1.37	1.02	1.84	0.04	1.42	1.06	1.91	0.02
Asian or Pacific Islander	0.79	0.73	0.87	<0.001	0.83	0.76	0.91	<0.001

Figure 4.3.

Patient-Related: Ethnicity Logistic Regression Results

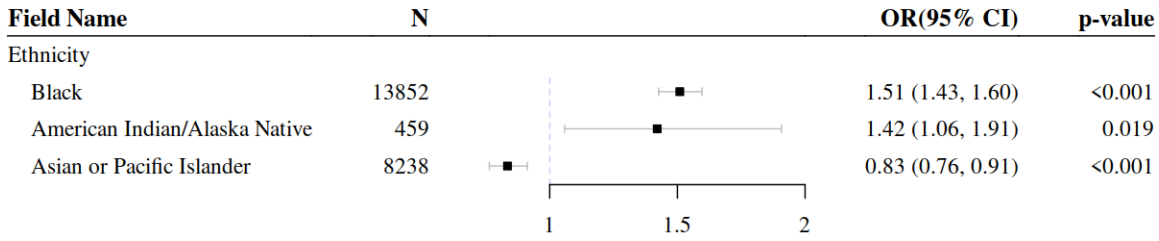


Table 4.7.

Patient-Related: Psychological Symptoms Logistic Regression Results

	Univariate Analysis	Multivariate Analysis

Factors	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Anxiety (Y)	1.29	1.22	1.36	<0.001	1.15	1.08	1. 23	<0.001
Anxiety (N)	0.88	0.84	0.91	<0.001	-	-	-	-
Depression (Y)	1.5	1.42	1.58	<0.001	1.49	1.39	1.59	<0.001
Depression (N)	0.83	0.79	0.86	<0.001	-	-	-	-

Figure 4.4.

Patient-Related: Psychological Symptoms Logistic Regression Results

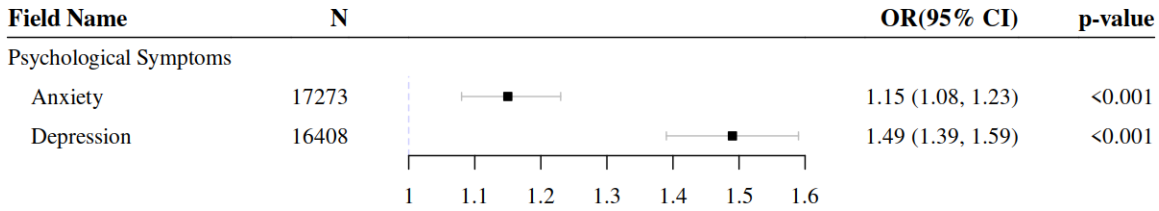


Table 4.8.

Patient-Related: Cognitive Issues Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Alzheimer's (dementia) Disease (Y)	1.73	1.63	1.84	<0.001	1.76	1.63	1.89	<0.001
Alzheimer's (dementia) Disease (N)	0.85	0.82	0.88	<0.001	-	-	-	-
Brain Damage (Y)	1.82	1.29	2.56	<0.001	1.53	1.06	2.2	0.02
Brain	0.96	0.93	1	0.05	-	-	-	-

Damage (N)								
Intellectual Disabilities (Y)	0.76	0.44	1.3	0.31	0.54	0.29	1	0.05
Intellectual Disabilities (N)	0.97	0.93	1.01	0.10	-	-	-	-
Learning Disabilities (Y)	2.07	1.23	3.47	0.01	1.63	0.9	2.96	0.11
Learning Disabilities (N)	0.97	0.93	1	0.07	-	-	-	-

Figure 4.5.

Patient-Related: Cognitive Logistic Regression Results

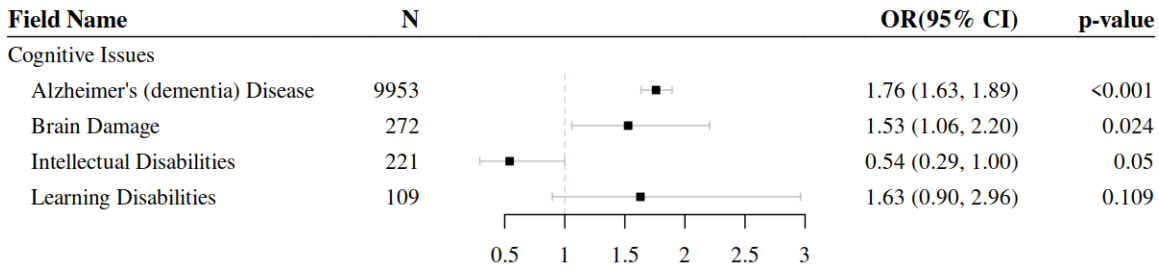


Table 4.9.

Patient-Related: Psychological Diseases Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
ADHD and Other Conduct Disorder (Y)	2.11	1.55	2.87	<0.001	1.65	1.17	2.32	<0.01

ADHD and Other Conduct Disorder (N)	0.96	0.92	1	0.04	-	-	-	-
Bipolar Disorder (Y)	1.79	1.56	2.05	<0.001	1.54	1.31	1.8	<0.001
Bipolar Disorder (N)	0.94	0.9	0.98	<0.01	-	-	-	-
Personality Disorders (Y)	1.5	1.25	1.81	<0.001	1.42	1.16	1.74	<0.001
Personality Disorders (N)	0.95	0.92	0.99	0.02	-	-	-	-
PTSD (Y)	1.85	1.38	2.48	<0.001	1.5	1.07	2.11	0.02
PTSD (N)	0.96	0.93	1	0.04	-	-	-	-
Schizophrenia and Related Conditions (Y)	1.88	1.61	2.18	<0.001	1.54	1.29	1.85	<0.001
Schizophrenia and Related Conditions (N)	0.94	0.91	0.98	<0.01	-	-	-	-

Figure 4.6.

Patient-Related: Psychological Diseases Logistic Regression Results

Field Name	N	OR(95% CI)	p-value
Psychological Diseases			
ADHD and Other Conduct Disorder	303	1.65 (1.17, 2.32)	0.004
Bipolar Disorder	1820	1.54 (1.31, 1.80)	<0.001
Personality Disorders	1076	1.42 (1.16, 1.74)	<0.001
PTSD	367	1.50 (1.07, 2.11)	0.018
Schizophrenia and Related Conditions	1387	1.54 (1.29, 1.85)	<0.001

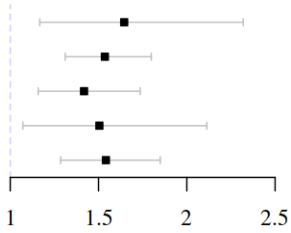


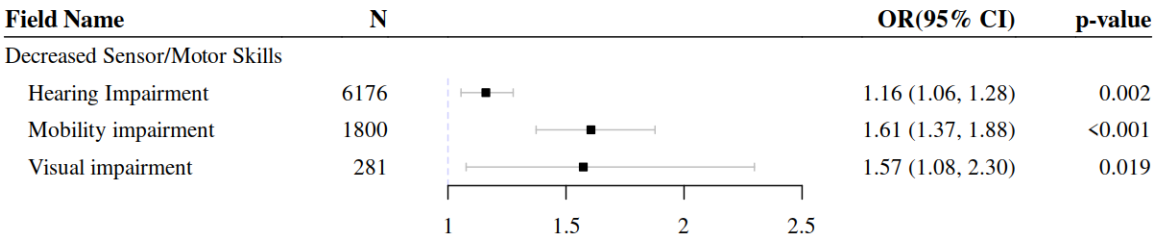
Table 4.10.

Patient-Related: Decreased Sensory/Motor Skills Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Hearing Impairment (Y)	1.14	1.04	1.24	0.01	1.16	1.06	1.28	<0.01
Hearing Impairment (N)	0.95	0.91	0.98	0.01	-	-	-	-
Mobility impairment (Y)	1.62	1.41	1.87	<0.001	1.61	1.37	1.88	<0.001
Mobility impairment (N)	0.94	0.91	0.98	<0.01	-	-	-	-
Visual impairment (Y)	1.64	1.16	2.33	0.01	1.57	1.08	2.3	0.02
Visual impairment (N)	0.96	0.93	1	0.054	-	-	-	-

Figure 4.7.

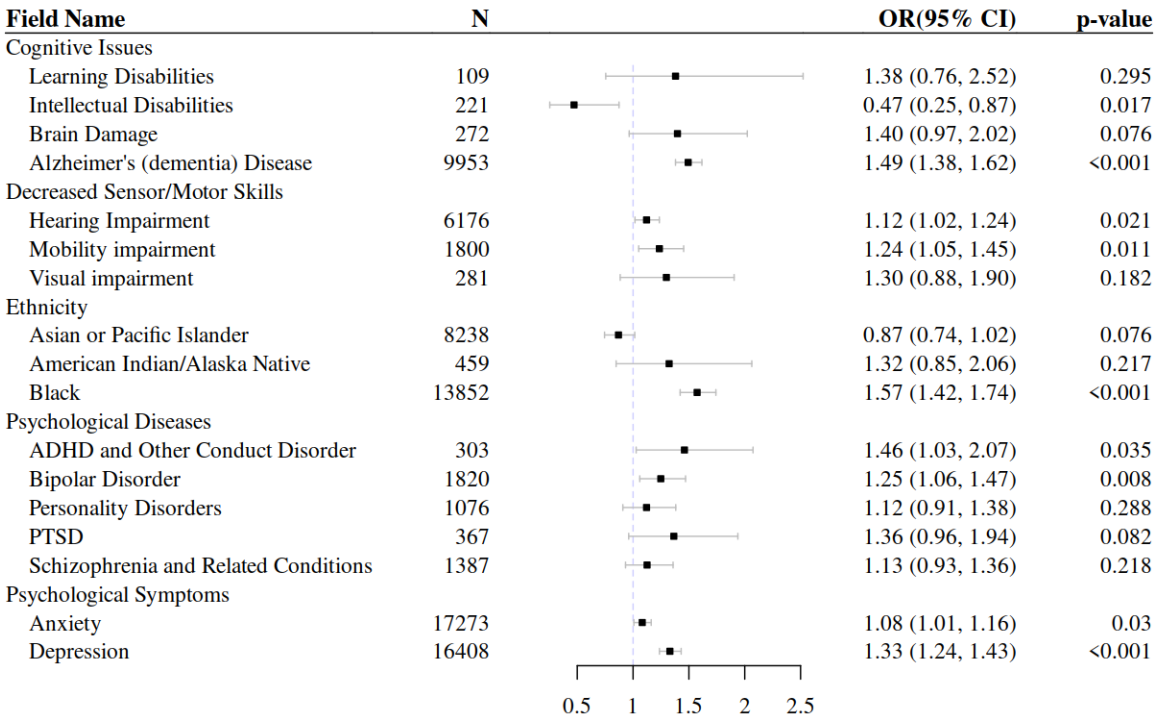
Patient-Related: Decreased Sensory/Motor Skills Logistic Regression Results



All patient-related variables were able to be analyzed together (Figure 4.6). Most patient-related factors (psychological symptoms, psychological diseases, cognitive issues, decreased sensory/motor skills) were positively associated with OET-NA except learning disability. However, still having Alzheimer, ADHD, and mobility impairment were strongest OET-NA factor as our previous each univariate and multivariate results.

Figure 4.8.

Patient-Related Factor Multivariate Regression Results



Socioeconomic-Related Factors

Among socioeconomic-related factors identified in the previous chapters, social and environmental factors such as marriage, lifestyle, and living status are analyzed here. AOR was calculated based on the 81,440 samples indexing patient's marital status in the SEER Cancer database (Table 4.11) using the binary logistic regression analysis. Other available samples were described on each figure (Figure 4.7, 4.8, 4.9, and 4.10). The sample size for marital status was relatively small due to the large number of missing data from the Medicare database. The AOR analysis eliminated all patients who did not have marital status data. Thus, due to its small sample size, marital status results cannot be generalized to the Medicare Part D patient population. Reference groups are selected as follows: (a) the married

living in metropolitan areas and (b) no psychological conditions. These reference variables were selected due to the significant amount of data points, allowing the investigation of different patient-related factors on OET-NA. In univariate analysis, the not-married factor (Single, Separated, and Divorced) was a determinant of OET-NA; however, multivariate analysis showed all the data were statistically insignificant to conclude this result (Table 4.11). Interestingly, all lifestyle factors were positively correlated with OET-NA. Opioid (AOR 1.94; 95% CI 1.55-2.44; p <0.001) and alcohol usage (AOR 1.71; 95% CI 1.37-2.14; p <0.001), 94% and 71%, respectively, were more likely to be present in OET-NA groups compared to adherent patients (Table 4.12). Patients' living status, whether urban or rural, were not statistically significantly correlated with OET-NA (Table 4.13).

Table 4.11.

Social-Related: Marital Status Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Single (never married)	1.2	1.11	1.3	<0.001	1.3	1.2	1.41	<0.001
Married	0.82	0.78	0.86	<0.001	-	-	-	-
Separated	1.3	0.99	1.7	0.06	1.46	1.11	1.91	0.01
Divorced	1.17	1.08	1.25	<0.001	1.27	1.17	1.37	<0.001
Widowed	1.06	1	1.12	0.06	1.16	1.09	1.23	<0.001

Figure 4.9.

Social-Related: Marital Status Logistic Regression Results

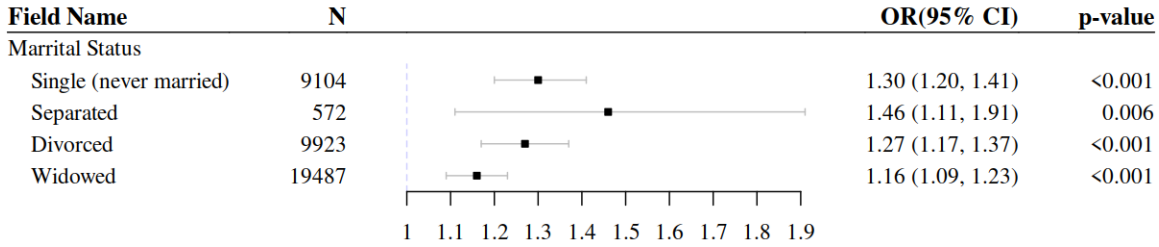


Table 4.12.

Social-Related: Lifestyle Status Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Alcohol use (Y)	1.85	1.51	2.27	<0.001	1.71	1.37	2.14	<0.001
Alcohol use (N)	0.95	0.92	0.99	0.01	-	-	-	-
Drug use (Y)	1.59	1.37	1.85	<0.001	0.94	0.76	1.17	0.57
Drug use (N)	0.95	0.91	0.99	0.01	-	-	-	-
Opioid drug use (Y)	1.96	1.68	2.3	<0.001	1.94	1.55	2.44	<0.001
Opioid drug use (N)	0.94	0.91	0.98	0.00	-	-	-	-
Opioid use for MAT (Y)	2.7	1.79	4.08	<0.001	0.85	0.43	1.72	0.66
Opioid use for MAT (N)	0.97	0.93	1	0.08	-	-	-	-
Tobacco use (Y)	1.49	1.36	1.64	<0.001	1.43	1.29	1.6	<0.001

Tobacco use (N)	0.93	0.89	0.96	<0.001	-	-	-	-

* MAT = Medication-Assisted Treatment

Figure 4.10.

Social-Related: Lifestyle Status Logistic Regression Results

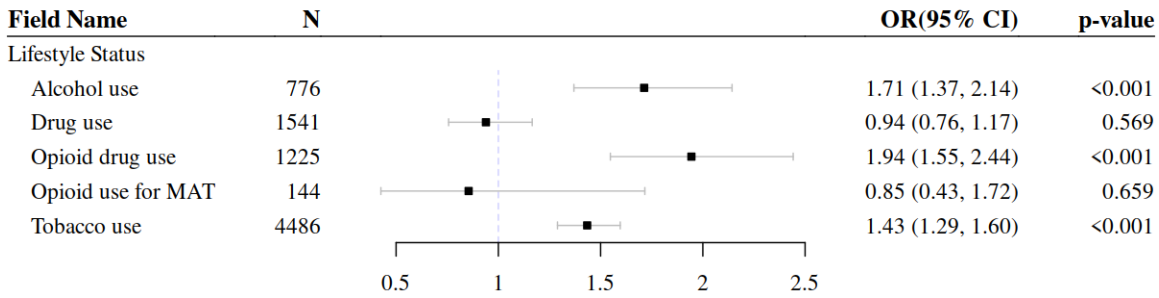


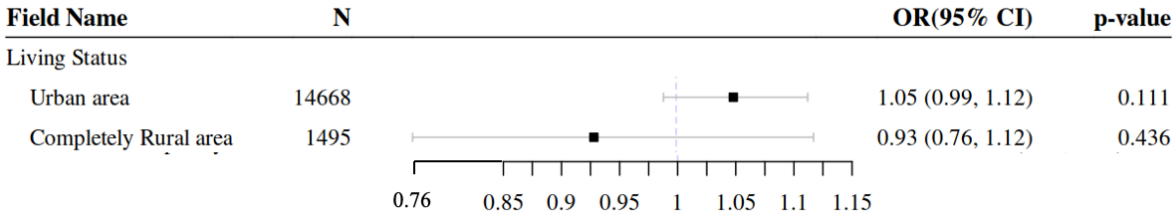
Table 4.13.

Environmental-Related: Living Status Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Metro area	0.96	0.91	1.02	0.20	-	-	-	-
Urban area	1.05	0.99	1.12	0.11	1.05	0.99	1.12	0.111
Completely Rural area	0.92	0.76	1.12	0.40	0.93	0.76	1.12	0.44

Figure 4.11.

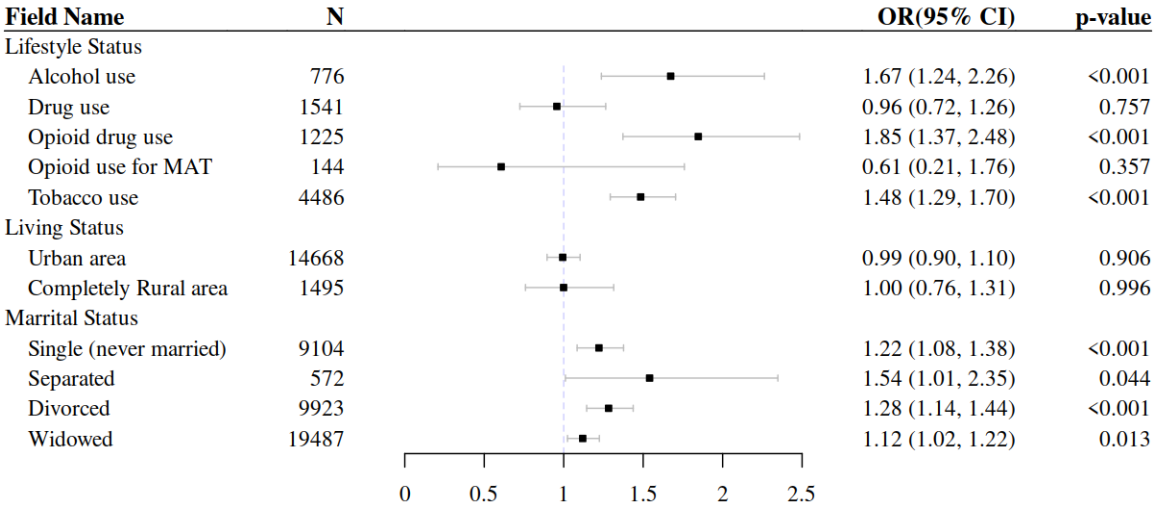
Environmental-Related: Living Status Logistic Regression Results



All socioeconomic-related variables were able to be analyzed together (Figure 4.10). Factors identified in previous analysis (Figure 4.7-9) appeared once again. (a) Living in rural areas, (b) using alcohol, drugs, and tobacco, (c) and unmarried status were all positively associated with OET-NA. This analysis still showed the same trends of previous univariate and multivariate analysis.

Figure 4.12.

Socioeconomic-Related Logistic Regression Results



Therapy-Related Factors

With respect to therapy-related factors, data describing medication regimens, therapy combinations, and switching regimens were retrieved. 207,618 patients' medication regimen was pulled from the SEER cancer database without any discrepancies in the PDESAF database (Table 4.14); however, therapy combinations (systemic, surgical, radiation) were only available in 85,845 of 141,457 patients in the SEER Cancer database (Table 4.15). AOR was calculated among patients who shared therapy types. Three other variables were assigned as reference for each category of multivariate analysis: having systemic therapy after surgery, radiation after surgery, and no drug therapy problems respectively (Table 4.14, and 4.15). These variables represent the most common course of therapy that the majority of patients were taking. The strongest determinant of OET-NA was a switched medication regimen (AOR 2.65; 95% CI 2.45-2.87; p <0.001) (Table 4.14). Patients having systemic chemo before surgical therapy were 19% more likely to have OET-NA (AOR 1.19; 95% CI 1.01-1.39; p <0.001) when compared to other systemic/surgical therapy combinations. Patients having radiation combination therapy were 100% more likely to have OET-NA (AOR 2.00; 95% CI 1.27-3.14; p =0.003) when compared to other radiation/surgical therapy combinations (Table 4.14). In univariate analysis, there was a positive effect on OET-NA when patients experience a drug therapy problem (DTP), which is a variable describing the number of drug therapy problem resolutions with prescribers resulting from recommendations made to patient's prescriber(s). In other words, DTP counts explain the number of drug problems patients previously experienced. Specifically, if a patient had more than four DTP (AOR 1.96; 95% CI 0.81-4.74; p =0.134), they were more likely to be non-adherent, but this result was statistically not significant (Table 4.15).

Table 4.14.

Therapy-Related: Medication Regimens and Therapy Combinations Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Medication Regimen								
OET medication switched (Y)	2.58	2.42	2.74	<0.001	2.65	2.45	2.87	<0.001
OET medication switched (N)	0.39	0.36	0.41	<0.001	-	-	-	-
Systemic and Surgical Therapy								
No systemic chemo and/or surgical therapy	1.11	1.05	1.18	<0.001	1.14	1.08	1.22	<0.001
Systemic therapy before surgery	1.17	1	1.37	0.05	1.19	1.01	1.4	0.04
Systemic therapy after surgery	0.88	0.83	0.92	<0.001	-	-	-	-
Systemic therapy both before and after surgery	1.11	0.97	1.27	0.13	1.13	0.98	1.3	0.09
Intraoperative systemic therapy	0.98	0.23	4.14	0.97	0.99	0.23	4.24	0.99
Intraoperative systemic therapy with other therapy	0.66	0.16	2.75	0.57	0.66	0.16	2.76	0.57

Surgery both before and after systemic therapy	1.18	0.9	1.56	0.23	1.22	0.92	1.6	0.17
Sequence unknown, but both surgery and systemic therapy were given	1.04	0.37	2.91	0.93	1.05	0.37	2.95	0.93
Radiation and Surgical Therapy								
No radiation and /or surgery	1.02	0.97	1.07	0.35	-	-	-	-
Radiation before surgery	2.12	1.36	3.31	<0.001	2.00	1.34	3.14	<0.01
Radiation after surgery	0.97	0.93	1.02	0.3	1.02	0.96	1.07	0.55
Radiation both before and after surgery	1.01	0.46	2.18	0.98	0.98	0.45	2.14	0.97
Intraoperative radiation	1.02	0.79	1.3	0.90	1.03	0.8	1.33	0.80
Intraoperative radiation with other radiation given	0.64	0.34	1.22	0.18	0.68	0.36	1.3	0.25
Sequence unknown, but both surgery and radiation were given	0.33	0.05	2.41	0.28	0.34	0.05	2.46	0.28

Figure 4.13.

Therapy-Related: Medication Regimens and Therapy Combinations Logistic Regression Results

Field Name	N	OR(95% CI)	p-value
Medication Regimen			
OET medication switched	7607	2.65 (2.45, 2.87)	<0.001
Radiation & Surgical Therapy			
Radiation before surgery	145	2.00 (1.27, 3.14)	0.003
Radiation after surgery	42154	1.02 (0.96, 1.07)	0.549
Radiation both before and after surgery	85	0.98 (0.45, 2.14)	0.968
Intraoperative radiation	832	1.03 (0.80, 1.33)	0.794
Intraoperative radiation with other radiation given	185	0.68 (0.36, 1.30)	0.243
Sequence unknown, surgery & radiation given	35	0.34 (0.05, 2.46)	0.284
Systemic & Surgical Therapy			
No systemic chemo and/or surgical therapy	21613	1.14 (1.08, 1.22)	<0.001
Systemic therapy before surgery	1870	1.19 (1.01, 1.39)	0.035
Systemic therapy both before and after surgery	2605	1.13 (0.98, 1.30)	0.085
Intraoperative systemic therapy	25	0.99 (0.23, 4.24)	0.991
Intraoperative systemic therapy with other therapy	36	0.66 (0.16, 2.76)	0.57
Surgery both before and after systemic therapy	599	1.21 (0.92, 1.60)	0.17
Sequence unknown, surgery & systemic therapy given	47	1.05 (0.37, 2.95)	0.928

Table 4.15.

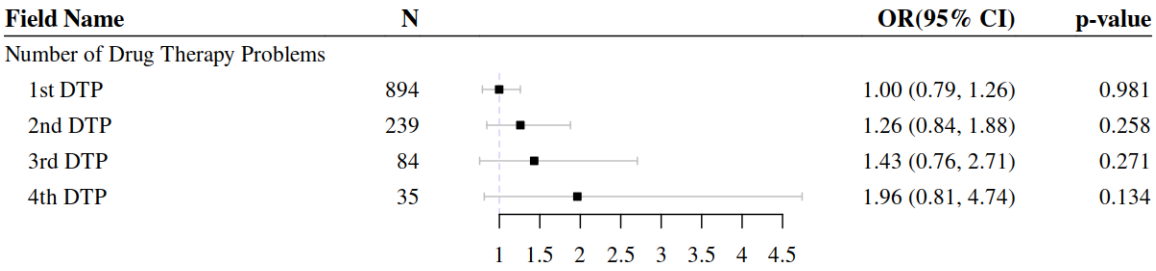
Therapy-Related: Number of Drug Therapy Problem Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
No Drug Therapy problem	0.92	0.76	1.12	0.41	-	-	-	-
1st Drug Therapy problem	0.99	0.78	1.25	0.91	1.0	0.79	1.26	0.98
2nd Drug Therapy problem	1.25	0.84	1.87	0.27	1.26	0.8	1.99	0.31
3rd Drug Therapy	1.42	0.75	2.69	0.28	1.44	0.74	2.83	0.29

problem								
4th Drug Therapy problem	1.95	0.81	4.71	0.14	1.85	0.75	4.57	0.18

Figure 4.14.

Therapy-Related: Number of Drug Therapy Problem Logistic Regression Results

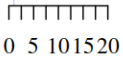


All therapy-related variables were able to be analyzed together (Figure 4.13). Only switching OET medication (Prescribed medication was changed) was positively associated with OET-NA. This analysis still showed the same trends of previous univariate and multivariate analysis except radiation therapy sequence due to small size of samples. From attenuating the variance effects of small samples with the entire therapy factor, I found that a higher number of DTP is associated with OET-NA that was not clearly presented in univariate or small multivariate analysis.

Figure 4.15.

Therapy-Related Factors: Multivariate Logistic Regression Results

Field Name	N	OR(95% CI)	p-value
Medication Regimen			
OET medication switched	7607	1.37 (0.93, 2.01)	0.11
Number of Drug Therapy Problems			
1st DTP	894	0.97 (0.71, 1.33)	0.85
2nd DTP	239	0.89 (0.46, 1.71)	0.729
3rd DTP	84	1.70 (0.71, 4.06)	0.235
4th DTP	35	2.94 (1.08, 8.02)	0.035
Radiation & Surgical Therapy			
Radiation after surgery	42154	0.93 (0.77, 1.11)	0.409
Intraoperative radiation	832	0.88 (0.31, 2.46)	0.805
Intraoperative radiation with other radiation given	185	0.94 (0.12, 7.31)	0.952
Radiation before surgery	145	2.79 (0.56, 13.83)	0.208
Systemic & Surgical Therapy			
Surgery both before and after systemic therapy	599	1.26 (0.49, 3.20)	0.633
Sequence unknown, surgery & systemic therapy given	47	3.89 (0.74, 20.35)	0.108
Systemic therapy both before and after surgery	2605	1.31 (0.81, 2.11)	0.276
Systemic therapy before surgery	1870	1.05 (0.60, 1.86)	0.858
No systemic chemo and/or surgical therapy	21613	1.18 (0.97, 1.44)	0.09



Condition-Related Factors

Among condition-related factors in the previous chapters, I was able to retrieve disease characteristics and comorbidity factors among breast cancer patients in 2019. I conducted multivariate binary logistic regression analysis to calculate AOR with 129, 746 patient samples for stage of cancer in the SEER Cancer database (Table 4.16). Other available samples were described on each figure (Figure 4.15 and 4.16). The Stage I group variable and having no conditions were selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA except two conditions. Specifically, hypertension and hyperlipidemia conditions used not having these conditions as references since the majority of patients (more than 60%) were in having these conditions. Having cancer Stage II (AOR 1.1; 95% CI 1.05-

1.15; p <0.001) and Stage IV (AOR 1.38; 95% CI 1.21-1.58; p <0.001) were identified as determinants of OET-NA. Unfortunately, Stage III cancer data was not statistically significant and therefore could not be concluded in my analysis (Table 4.16).

Almost all comorbidities had a positive effect on OET-NA. Especially, having a hip fracture (AOR 2.21; 95% CI 1.79-2.72; p <0.001) and acute myocardial infarction (AMI) (AOR 1.38; 95% CI 1.06-1.80; p =0.016) are the strongest OET-NA determinants.

Table 4.16.

Condition- Related: Disease Characteristics Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Stage I	0.92	0.88	0.96	<0.001	-	-	-	-
Stage II	1.09	1.04	1.14	<0.001	1.1	1.05	1.15	<0.001
Stage III	1.03	0.93	1.14	0.60	1.07	0.96	1.18	0.21
Stage IV	1.37	1.2	1.56	<0.001	1.38	1.21	1.58	<0.001

Figure 4.16.

Condition- Related: Disease Characteristics Logistic Regression Results

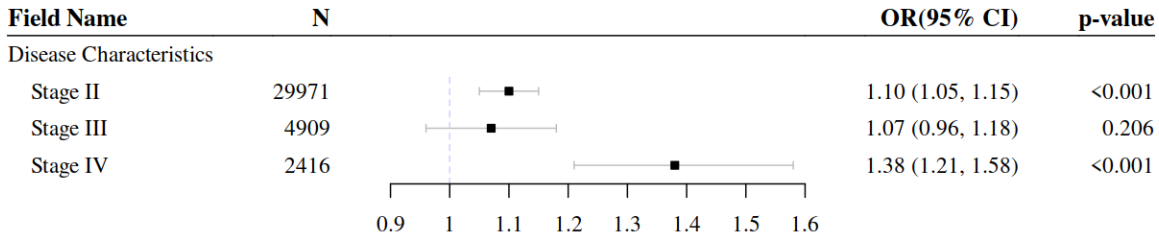


Table 4.17.

Condition-Related: Comorbidity Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
AMI (Y)	2.04	1.61	2.59	<0.001	1.38	1.06	1.8	0.02
AMI (N)	0.97	0.93	1.01	0.11	-	-	-	-
Anemia (Y)	1.33	1.27	1.39	<0.001	1.15	1.08	1.22	<0.001
Anemia (N)	0.84	0.8	0.87	<0.001	-	-	-	-
Asthma (Y)	1.23	1.13	1.35	<0.001	1.06	0.96	1.17	0.25
Asthma (N)	0.95	0.92	0.99	0.01	-	-	-	-
CHF (Y)	1.44	1.36	1.53	<0.001	1.13	1.04	1.22	<0.01
CHF (N)	0.87	0.83	0.9	<0.001	-	-	-	-
COPD (Y)	1.44	1.35	1.55	<0.001	1.2	1.1	1.3	<0.001
COPD (N)	0.9	0.86	0.93	<0.001	-	-	-	-
CKD (Y)	1.32	1.26	1.39	<0.001	1.06	0.99	1.14	0.09
CKD (N)	0.86	0.83	0.9	<0.001	-	-	-	-
Diabetes (Y)	1.22	1.17	1.28	<0.001	1.08	1.01	1.15	0.03
Diabetes (N)	0.88	0.84	0.91	<0.001	-	-	-	-
Epilepsy (Y)	1.79	1.53	2.09	<0.001	1.52	1.28	1.81	<0.001
Epilepsy (N)	0.94	0.91	0.98	<0.01	-	-	-	-
Fibromyalgia Chronic Pain and Fatigue (Y)	1.26	1.2	1.33	<0.001	1.2	1.13	1.28	<0.001
Fibromyalgia Chronic Pain and Fatigue (N)	0.86	0.83	0.9	<0.001	-	-	-	-
Hepatitis (Viral) (Y)	1.29	0.99	1.69	0.06	1.17	0.88	1.57	0.28
Hepatitis (Viral) (N)	0.96	0.93	1	0.05	-	-	-	-
Hip Fracture (Y)	2.83	2.33	3.44	<0.001	2.21	1.79	2.72	<0.001
Hip Fracture	0.96	0.92	0.99	0.02	-	-	-	-

(N)								
HIV/AIDS (Y)	0.31	0.04	2.26	0.25	0.4	0.05	2.98	0.37
HIV/AIDS (N)	0.97	0.93	1.01	0.09	-	-	-	-
Hyperlipidemia (Y)	1.02	0.98	1.06	0.32	-	-	-	-
Hyperlipidemia (N)	0.97	0.93	1.02	0.27	1.09	1.03	1.17	<0.01
Hypertension (Y)	1.09	1.04	1.13	<0.001	-	-	-	-
Hypertension (N)	0.9	0.86	0.96	<0.001	1.08	1	1.15	0.04
Hypothyroid (Y)	1.12	1.06	1.18	<0.001	1.04	0.98	1.11	0.21
Hypothyroid (N)	0.94	0.9	0.98	<0.01	-	-	-	-
Leukemia and lymphomas (Y)	1.2	1.01	1.43	0.04	1.03	0.85	1.24	0.79
Leukemia and lymphomas (N)	0.96	0.93	1	0.05	-	-	-	-
Liver Diseases (Y)	1.25	1.15	1.37	<0.001	1.12	1.01	1.24	0.03
Liver Diseases (N)	0.94	0.9	0.97	<0.001	-	-	-	-
Migraine and Other Chronic Headache (Y)	1.3	1.15	1.47	<0.001	1.2	1.05	1.38	0.01
Migraine and Other Chronic Headache (N)	0.95	0.92	0.99	0.01	-	-	-	-
Obesity (Y)	1.18	1.12	1.24	<0.001	1.1	1.04	1.18	<0.01

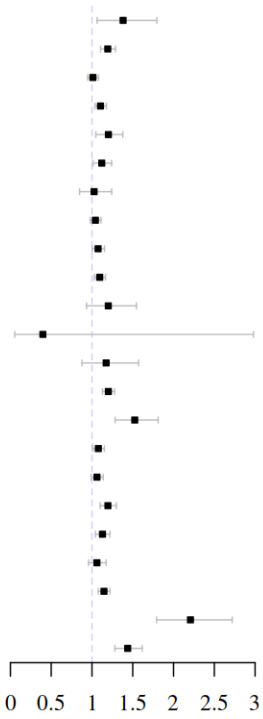
Obesity (N)	0.89	0.86	0.93	<0.001	-	-	-	-
Osteoporosis (Y)	1.02	0.97	1.08	0.45	1.01	0.95	1.08	0.73
Osteoporosis (N)	0.97	0.94	1.01	0.20	-	-	-	-
PVD (Y)	1.42	1.33	1.51	<0.001	1.19	1.11	1.29	<0.001
PVD (N)	0.87	0.84	0.9	<0.001	-	-	-	-
Spinal Injury (Y)	1.69	1.34	2.12	<0.001	1.2	0.93	1.54	0.16
Spinal Injury (N)	0.96	0.92	0.99	0.03	-	-	-	-
Ulcers (Y)	1.94	1.76	2.14	<0.001	1.44	1.28	1.61	<0.001
Ulcers (N)	0.91	0.87	0.94	<0.001	-	-	-	-

Abbreviations are acute myocardial infarction (AMI) hyperlipidemia (HLD) hypertension (HTN), human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS), congested heart failure (CHF), peripheral vascular disease (PVD)

Figure 4.17.

Condition-Related: Comorbidity Logistic Regression Results

Field Name	N	OR(95% CI)	p-value
Comorbidity			
AMI	520	1.38 (1.06, 1.80)	0.016
PVD	11560	1.19 (1.11, 1.29)	<0.001
Osteoporosis	17354	1.01 (0.95, 1.08)	0.728
Obesity	21448	1.10 (1.04, 1.18)	0.002
Migraine and Other Chronic Headache	2683	1.20 (1.05, 1.38)	0.009
Liver Diseases	5435	1.12 (1.01, 1.24)	0.029
Leukemia and lymphomas	1465	1.03 (0.85, 1.24)	0.791
Hypothyroid	18832	1.04 (0.98, 1.11)	0.205
No Hypertension	20165	1.08 (1.00, 1.15)	0.042
No Hyperlipidemia	27092	1.09 (1.03, 1.17)	0.004
Spinal Injury	650	1.20 (0.93, 1.54)	0.156
HIV/AIDS	37	0.40 (0.05, 2.98)	0.37
Hepatitis (Viral)	570	1.17 (0.88, 1.57)	0.282
Fibromyalgia Chronic Pain and Fatigue	19968	1.20 (1.13, 1.28)	<0.001
Epilepsy	1370	1.52 (1.28, 1.81)	<0.001
Diabetes	25387	1.08 (1.01, 1.15)	0.026
CKD	21393	1.06 (0.99, 1.14)	0.094
COPD	8825	1.20 (1.10, 1.30)	<0.001
CHF	12704	1.13 (1.04, 1.22)	0.002
Asthma	5646	1.06 (0.96, 1.17)	0.254
Anemia	24419	1.15 (1.08, 1.22)	<0.001
Hip Fracture	642	2.21 (1.79, 2.72)	<0.001
Ulcers	3368	1.44 (1.28, 1.61)	<0.001



Multivariate analysis by utilizing all these possible condition-related factors were not able to be computed due to increased number of variables with poor sample distribution across each variable.

Health Care Team/System-Related Factors

Among health care team/system-related factors in the previous chapters, I was able to retrieve health care team/system issues. Unfortunately, only 275 patients' data were available in Comprehensive Medication Review (CMR) in the PDEMTM database, and 82,705 patients' data for provider's partnership status category, 84,269 for deductible insurance information, and 83,827 for co-insurance information were retrieved to see the healthcare

system issues from the NCH database. I calculated AOR based on available data, but it cannot be generalized to the entire breast cancer population in 2019. The CMR nurse practitioner, solo practitioner, having no coinsurance payments group variables and having no conditions were selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

The CMR provider data (Table 4.18) did not show any statistically significant results. Unfortunately, OET-NA patients' healthcare services were likely to subject to deductible (AOR 1.25; 95% CI 1.16-1.35; p <0.001), but this data cannot be generalized since it is coming from 84,269 out of entire 141,457 (Table 4.20). Type of provider's partnership is a status of the provider's working condition such as whether they work alone or in a group clinic or institution. Especially, identifying solo vs small or larger group practices were the main focus of this variable (Table 4.19). Patients seeing multiple providers from group practitioner type clinic (AOR 1.03; 95% CI 0.97-1.1; p =0.36) and institution (AOR 1.54; 95% CI 1.34-1.77; p <0.001) determinants that were 3% and 34%, respectively, were more likely to be present in OET-NA groups compared to the solo practitioner group (Table 4.19).

Table 4.18.

Health Care Team-Related: CMR Review Reviewer Type Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
CMR provider-Physician	0.67	0.09	5.11	0.70	0.6	0.07	4.89	0.64
CMR provider-Registered Nurse	0.73	0.29	1.83	0.51	0.65	0.23	1.85	0.42

CMR provider-Licensed practical nurse	0.9	0.21	3.82	0.88	0.73	0.16	3.41	0.69
CMR provider-Nurse practitioner	1.13	0.67	1.91	0.64	-	-	-	-
CMR provider-Pharmacist	0.72	0.09	5.53	0.76	0.65	0.08	5.29	0.69

Figure 4.18.

Health Care Team-Related: CMR Reviewer Type Logistic Regression Results

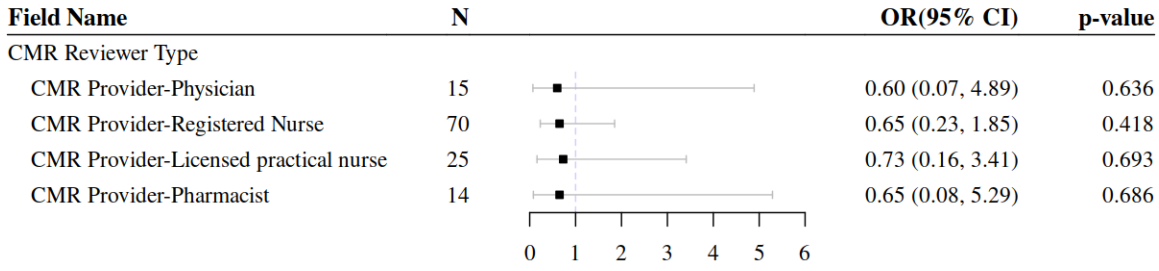


Table 4.19.

Health Care Team-Related: Provider Partnership Status Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95%CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95%CI	p-value
Group Practitioners in Clinic	1.05	0.97	1.13	0.20	1.03	0.97	1.1	0.36
Solo	1.01	0.97	1.06	0.59	-	-	-	-

Practitioners Institution providers (share patients)	1.54	1.31	1.8	<0.001	1.54	1.34	1.77	<0.001

Figure 4.19.

Health Care Team-Related: Provider Partnership Status Logistic Regression Results

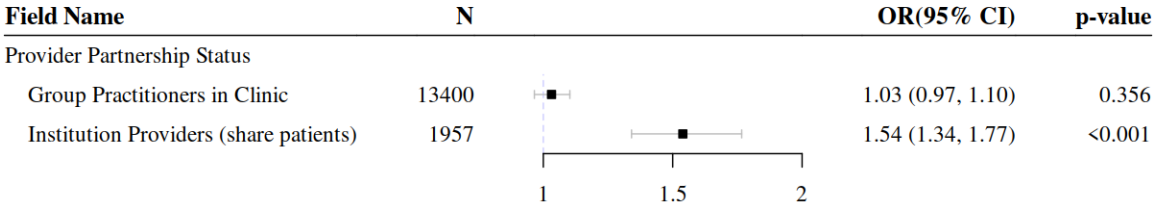


Table 4.20.

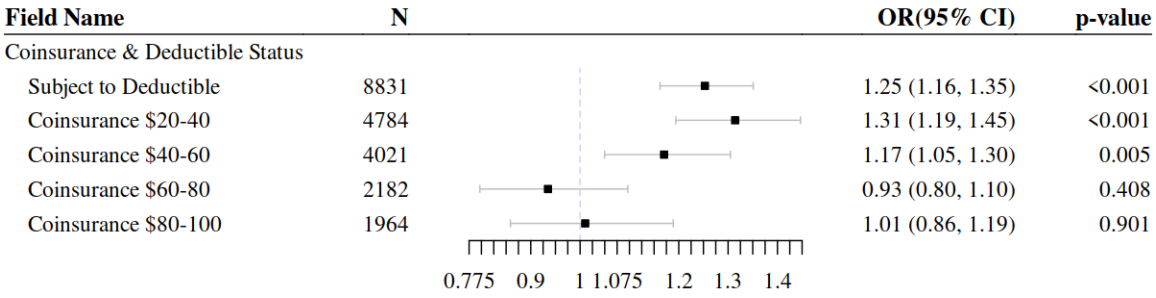
Health Care System-Related: Co-insurance and Deductible Status Logistic Regression Results

Factors	Univariate Analysis				Multivariate Analysis			
	Unadjusted OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Coinsurance amount $0-20	0.97	0.93	1.02	0.26	-	-	-	-
Coinsurance amount $20-40	1.42	1.25	1.62	<0.001	1.31	1.19	1.45	<0.001
Coinsurance amount $40-60	1.34	1.16	1.54	<0.001	1.17	1.05	1.3	0.01
Coinsurance amount $60-80	0.97	0.76	1.25	0.84	0.93	0.8	1.1	0.41

Coinsurance amount $80-100	0.94	0.72	1.24	0.66	1.01	0.86	1.19	0.90
Health care service subject to deductible (Y)	1.26	1.17	1.35	<0.001	1.25	1.16	1.35	<0.001
Health care service subject to deductible (N)	0.8	0.74	0.86	<0.001	-	-	-	-

Figure 4.20.

Health Care System-Related: Co-insurance and Deductible Status Logistic Regression Results



Multivariate analysis by utilizing all these possible health care team/system-related factors were not able to be computed due to increased number of variables with poor sample distribution across each variable.

Post-Hoc Analysis

This section is constructed to present the joint influences between multi-level determinants that I have discussed in research question number 2. Previously, I focused on

each-level in detail to see which factors were impacting OET-NA among the chosen category of each patient-related, socioeconomic-related, therapy-related, condition-related and healthcare team/system-related levels. Hierarchical multivariate logistic regression is utilized to analyze the selected variables. I will present how these variables were selected into the final analysis to show the importance of each variable's influence even though it is classified in different multi-level systems.

Selected Variables

A total of 40 variables were selected for this post-hoc analysis from the multi-levels. These variables were identified as the most important factors based on my previous analysis results and my literature review in Chapter 2.

Patient-Related Variables

Patient's Ethnicity. This variable has four categorical groups including White, Black, American Indian/Alaska Native, and Asian or Pacific Islander. Patients' ethnic groups were one of the most frequently recognized factors for medication-NA (Banegas et al., 2018; Cedillo-Couvert et al., 2018; Chen et al., 2009; Darkow et al., 2007; Halpern et al., 2009; Lee & Salloum, 2015; Mathes et al.,2014b; Molnar et al., 2016; Sheppard et al., 2019). The White group is selected as a reference group to capture the full range of potential effects on OET-NA that could exist. Also, the White group had the most significant amount of data points to support our analysis as a reference.

Psychological Factors. The two most frequently recognized psychological factors in previous review studies were anxiety and depression for breast cancer patients (Chew et al., 2015; Crawshaw et al., 2016; Mathes et al., 2014b; Santos et al., 2019; Yoon et al., 2018; Yussof et al., 2022). Not having these conditions (anxiety and depression) were selected as a

reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Socioeconomic-Related Variables

Marital Status. This variable has five categorical groups: single, married, separated, divorced, and widowed. Marital status is also recognized as an important factor for medication-NA even with breast cancer populations (Geissler et al., 2017; Kaye, 2016; Mohamed & Elamin, 2020; Molnar et al., 2016; Tan et al., 2017; Xu & Wang, 2019). The Married variable was chosen for a reference due to the significant amount of data points that allow us to compare OET-NA effects more easily.

Lifestyle Factors. Using alcohol and drugs is a lifestyle factor that is frequently recognized as a significant determinant for general medication-NA (Fernandez-Lazaro et al., 2019; Mathes et al., 2014; Nonogaki et al., 2019); however, several cancer studies failed to show a strong relationship between this factor and cancer medication-NA (Mislang et al., 2017; Verbrugghe et al., 2013). Therefore, this is an important portion of our analysis since we have less supportive evidence for lifestyle factors especially in cancer populations. Not having these conditions (alcohol, drug, and tobacco respectively) is selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Living Status. Living status is categorized as metro, urban and rural areas. This is another important factor that has been discussed across different types of diseases including breast cancer (Addidja et al., 2018; Al-Noumani et al., 2017; Daniel et al., 2013; Dennis et al. 2010; Hussein et al., 2020; Nonogaki et al., 2019). Living in Metro areas is selected as a

reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Condition-Related Variables

Disease Characteristics. Stages of cancer were categorized as Stage I, Stage II, Stage III, and Stage IV. Several studies reported that certain stages of cancer were strongly related to medication-NA especially for breast cancer patients (Ali et al., 2022; Ma et al., 2021; Meneveau et al., 2020; Showalter et al., 2021; Tan et al., 2017). Stage I is selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Comorbidities. Four popular comorbidities were selected specifically for breast cancer patients including hyperlipidemia, hypertension, obesity, and osteoporosis. These comorbidities were frequently recognized as an important factor across all chronic diseases (Adidja et al., 2018; Crawshaw et al., 2016; Hussein et al., 2020; Gast et al. 2019; Ma et al., 2021; Yussof et al., 2022). Especially, many breast cancer patients with osteoporosis were struggling more to take OET medication since this therapy increases risk of bone loss and exacerbates osteoporosis (Perez et al., 2006). Not having these conditions (hyperlipidemia, hypertension, obesity, and osteoporosis respectively) were selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Therapy-Related Variables

In medication regimen category, two variables were included: (a) OET prescribed medication was changed, and (b) OET prescribed medication was not changed. These factors were more critically affecting cancer populations including breast cancer than other chronic

diseases (Marques & Pierin, 2008; Murphy et al., 2012; Yussof et al., 2022). Not switching OET medications (prescribed medication was not changed) is selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Health Care Team/System-Related Variables

Health Care Team Practice Characteristics. Three variables were included: (a) group practitioners in clinic, (b) solo practitioners and (c) institution providers who share patients. in this category. The solo-practitioners were selected as a reference group due to the significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA. Having multiple providers for one patient tends to increase medication-NA across diverse settings on different chronic diseases due to decreased interaction and difficulty making a good relationship with the patient (Geissler et al., 2017; Lebovits, 1990; Marques & Pierin, 2008; Moon et al., 2017; Toivonen et al., 2020; Kimmick et al., 2015).

Health Care System Characteristics. Two variables were included: (a) health care service subject to deductible and (b) health care service not subject to deductible. If a patient does not meet the Medicare deductible, the actual cost of payment that patient would be responsible for would increase. Thus, it will increase the burden of patients taking OET correctly and they were likely to be OET-NA. This is critical information for researchers to understand health care issues regarding OET-NA effects and this was confirmed in small size of data earlier in all chronic disease patients including breast cancer (Chen et al., 2009; Halpern et al., 2009; Mathes et al., 2014b; Murphy et al., 2012; Streeter et al., 2011). The variable, health care service subject to deductible, is selected as a reference group due to the

significant amount of data points compared to having these conditions to investigate these factors' effects on OET-NA.

Results of Analysis

The result of this analysis is available in Table 4.21. A total number of 3,930 patients were included in this analysis. Pseudo R-squared of this analysis was 0.023. Black ethnic group were identified as the most vulnerable populations (AOR 1.55; 95% CI 1.34-1.78; p <0.001). Moreover, patients who were obese (AOR 1.13; 95% CI 1.03-1.23; p =0.007), were diagnosed with Stage II cancer (AOR 1.12; 95% CI 1.02-1.22; p =0.013), were using alcohol (AOR 1.40; 95% CI 1.10-1.93; p =0.043), were using tobacco (AOR 1.41; 95% CI 1.22-1.63; p <0.001), were single (AOR 1.15; 95% CI 1.01-1.30; p =0.032), were divorced (AOR 1.17; 95% CI 1.04-1.32; p =0.01), switched prescribed OET medications (AOR 2.72; 95% CI 2.41-3.07; p <0.001), had multiple provider (AOR 1.26; 95% CI 1.01-1.56; p <0.001), and had depression (AOR 1.40; 95% CI 1.27-1.54; p <0.001) were more likely to be OET-NA. This post-hoc analysis result will be interpreted and discussed in detail in Chapter 5: Discussion section.

Table 4.21.

Post-Hoc Analysis to Explore Joint Influences of Multi-Level Determinants.

			Multivariate Analysis			
	Variables		Odd Ratio	Lower 95% CI	Upper 95% CI	p-value
Patient-Related Variables	Race/ Ethnicity	White	-	-	-	-
		Black	1.55	1.34	1.78	<0.001
		American Indian/Alaska Native	1.38	0.80	2.38	0.25
		Asian or Pacific Islander	0.94	0.78	1.12	0.47
		Anxiety (Y)	1.08	0.98	1.19	0.10

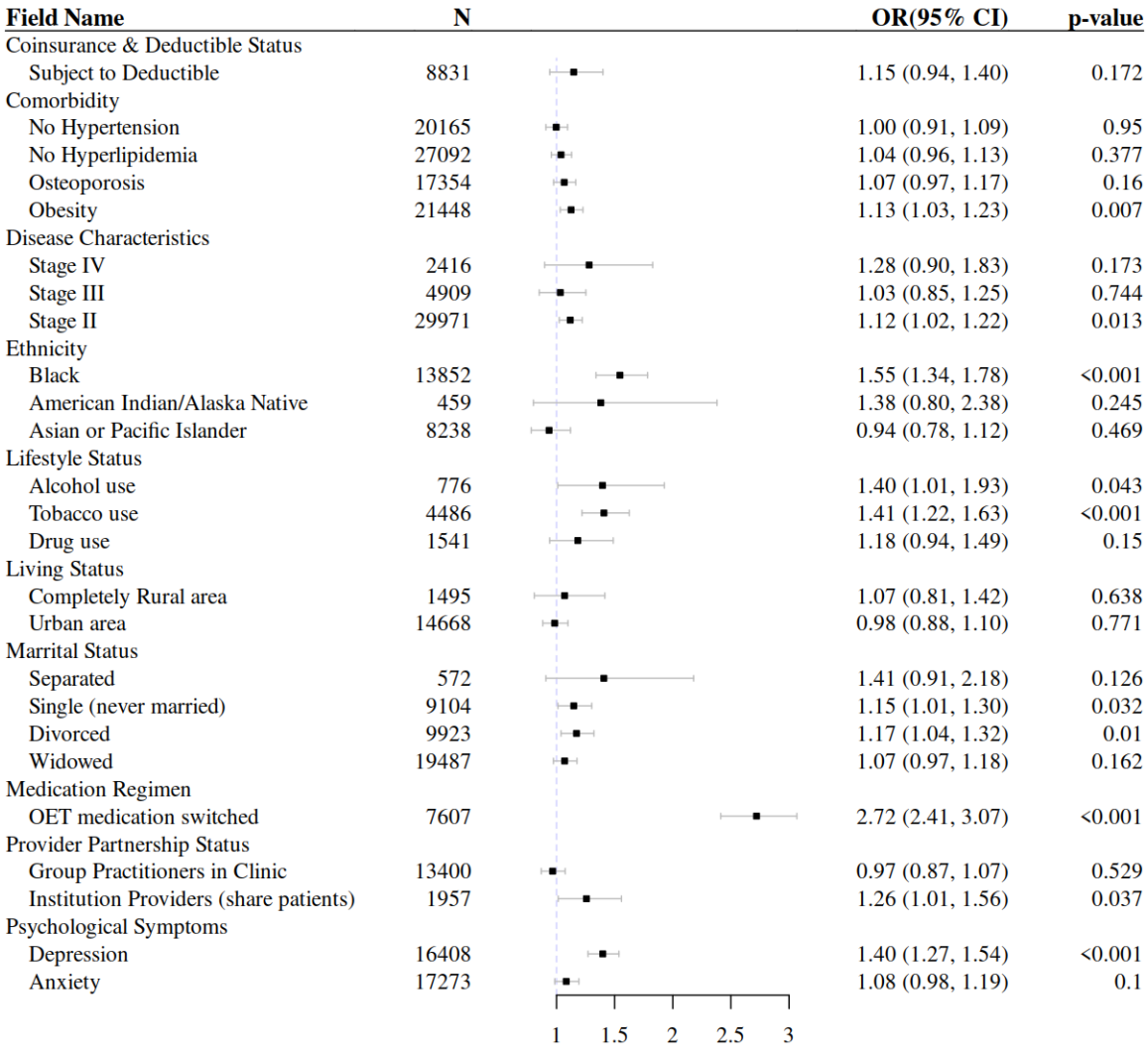
	Psychological Factors	Anxiety (N)	-	-	-	-
		Depression (Y)	1.40	1.27	1.54	<0.001
		Depression (N)	-	-	-	-
	Marriage Status	Single	1.15	1.01	1.30	0.03
		Married	-	-	-	-
		Separated	1.41	0.91	2.18	0.13
		Divorced	1.17	1.04	1.32	0.01
		Widowed	1.07	0.97	1.18	0.16
Socioeconomic Related Variables	Lifestyle Factor	Alcohol (Y)	1.40	1.01	1.93	0.04
		Alcohol (N)	-	-	-	-
		Drug (Y)	1.18	0.94	1.49	0.15
		Drug (N)	-	-	-	-
		Tobacco (Y)	1.41	1.22	1.63	<0.001
		Tobacco (N)	-	-	-	-
	Living Status	Metro area	-	-	-	-
		Urban area	0.98	0.88	1.10	0.77
		Rural area	1.07	0.81	1.42	0.64
	Disease characteristics	Stage I	-	-	-	-
		Stage II	1.12	1.02	1.22	0.01
		Stage III	1.03	0.85	1.25	0.74
		Stage IV	1.28	0.90	1.83	0.17
Condition-Related Variables	Comorbidities	Hyperlipidemia (Y)	-	-	-	-
		Hyperlipidemia (N)	1.04	0.96	1.13	0.38
		Hypertension (Y)	-	-	-	-
		Hypertension (N)	1.00	0.91	1.09	0.95
		Obesity (Y)	1.13	1.03	1.23	0.01
		Obesity (N)	-	-	-	-
		Osteoporosis (Y)	1.07	0.97	1.17	0.16
		Osteoporosis (N)	-	-	-	-
Therapy-Related Variables	Medication Regimen	OET medication switched (Y)	2.72	2.41	3.07	<0.001
		OET medication switched (N)	-	-	-	-
Health Care Team/ System-Related Variables	Healthcare team practice characteristics	Solo partitioner	-	-	-	-
		Group partitioner	0.97	0.87	1.07	0.53
		Institution providers (share patients)	1.26	1.01	1.56	0.037

	Healthcare system characteristics	Health care service subject to deductible (Y)	1.15	0.94	1.40	0.17
		Health care service subject to deductible (N)	-	-	-	-

[a]CMR = Comprehensive Medication Review

Figure. 4.21.

Post-Hoc Analysis to Explore Joint Influences of Multi-Level Determinants.



CHAPTER 5

DISCUSSION

Chapter 5 will present the discussion of a descriptive, correlational research study completed using bivariate logistic regression analysis with odds ratio. The purpose of this study was to identify the rate of OET-NA and find the patient-related, socioeconomic-related, therapy-related, condition-related, and healthcare team/system-related determinants of OET-NA for breast cancer patients 65 years of age or older. Chapter 5 will be followed by interpretation of findings, strengths, limitations, implications, future research, and conclusions.

Interpretation of Findings

Identifying OET-NA Rates

Based on information from the 2019 SEER Medicare database, I found that the OET-NA rate was 6.35% and the OET adherence rate was 93.65% among breast cancer patients (average age 73.16). The rates of OET medication adherence were 98.06% when using MPR as a measure, and 93.65% when using PDC as a measure. The rates of OET-NA were 1.94% when using MPR as a measure, and 6.35% when using PDC as a measure. The MPR OET-NA rates were 4.41%, which is lower than the PDC method. This result indicates that the MPR method of measurement created extra dates to lower the NA rates than the PDC method. It was simple to identify over-adherence since I have calculated the same information with two different methods but just applied a different method that allows overlapped dates. This is often referred to as over-adherence of which corresponds that many breast cancer patients were likely to pick their medications up earlier than suggested dates.

For example, when a patient picks up their medications earlier than the correct refill date, there would be extra dates unintentionally added into our calculations as an over-adherence. My results also showed that OET-NA rates were better than those for other types of medication because medication-NA rates were ranged from 2-30%. The NA rate for oral home-cancer-medications ranges from 3-85% (Bouwman et al., 2017; Hansen, 2012). Specifically, cytotoxic medication-NA rate was 10-50% (Hirao et al., 2017; Ruddy et al., 2009). In leukemia cases, medication-NA rates were ranged 6–35% in patients with acute lymphoid leukemia (ALL), and 20-53% in patients with chronic myeloid leukemia (CML) (Bouwman et al., 2017). However, even when medication-NA rates were identified as low (e.g., 6%), this small percentage of medication-NA can cause poor patient outcomes (i.e., increased mortality) especially when it is critical medication for their disease (Lee et al., 2021). Marin et al. (2010) emphasized cancer patients taking ≤90% of prescribed medications had clearly inferior major molecular response rates compared to adherent patients. Optimal medication adherence was highly associated with positive health outcomes among cancer patients (Bouwman et al., 2017). While skipping a dose of OET may not have the immediate consequences of other types of critical cancer medications, it still can be a dangerous problem because breast cancer is a more widespread issue for a longer period of time. This indicates that researchers must study more about long term OET-NA determinants to help this large population. With grown older adult populations, it is critical to understand the issues of OET-NA since previous statistics showed that the majority of the breast cancer population is older, as the median is 62 years of age and it presents a higher risk of mortality, especially for older women.

Multilevel Influenced Determinants of OET-NA

I will compare and contrast our findings to the available current studies in breast cancer and general chronic disease populations.

Table 5.1.

Patient-Related Discussion

Patient-Related	My Findings	Breast Cancer	Chronic Disease
Cognitive issues	Alzheimer's (dementia) disease (OR 1.49) (reference: not having these conditions)	Dementia	Forgetfulness Knowledge issues Dementia disease
Decreased Sensor/Motor skills	Hearing impairment (OR 1.12) Mobility impairment (OR 1.24) (reference: not having these conditions)	-	-
Ethnicity	*Black (OR 1.57) (reference: White)	Black, Not being White	Not being White
Psychological Disease	ADHD (OR 1.46) Bipolar Disorder (OR 1.25) (reference: not having these conditions)	Bipolar (protective for OET-NA)	Bipolar
Psychological Symptoms	Anxiety (OR 1.08) *Depression (OR 1.33) (reference: Not having these conditions)	Anxiety and Depression	Anxiety and Depression

Patient-related factors showed the way a patient's race, psychological symptoms and diseases, cognitive issues, and decreased sensory/motor skills affected their likelihood of OET-NA, which was in line with previous studies (Brett et al., 2018; Corter et al., 2018; Fleming et al., 2020; Hershman et al., 2016; Kimmick et al., 2015; Lambert et al., 2018;

Toivonen et al., 2020; Yussof et al., 2022). Concerning cognitive issues, Alzheimer's disease was one of the strongest factors for OET-NA, which had also been shown in breast cancer and chronic diseases studies with small sample sizes (Meneveau et al., 2020; Yussof et al., 2022). Cognitive issues were a major factor for medication-NA and were often correlated with forgetfulness (Al-Noumani et al., 2016; Bane et al., 2006; Colbert et al., 2013), knowledge issues (Fernandez-Lazaro et al., 2019), and all other dementia-related factors (Colbert et al., 2013; Seung et al., 2020).

In terms of decreased sensory/motor skills, hearing and mobility impairments were determinants of OET-NA in my findings; however, these specific impairments were not discussed in breast cancer and chronic disease populations in particular. Older patients have a higher risk of non-adherence due to decreased function in dexterity, mobility, hearing and vision (Arlt et al., 2008). These impairments are frequently ignored criteria: Jin et al. (2016) excluded older adults who had severe visual impairment and/or poor hearing because they were conducting a survey type of study that cannot be applied for patients with hearing and/or visual impairments.

Alternatively, some studies found that decreased sensory/motor skills can be investigated via focusing on the severity of impairment, and the complexity of self-management tasks (Smith et al., 2017). However, these studies typically have a small amount of evidence due to the need for a healthcare professional to be able to observe and report the medication taking behaviors. This leads to limited sample sizes and incoherent research designs that use subjective measures. Also, Smith's (2017) team mentioned that previous articles often related these sensory/motor skill impairments to cognitive issues (i.e., dementia) because deficits in cognitive processes may decrease older adults' medication

taking skill due to impairment of abilities in planning, organizing and executing medication management tasks.

In the ethnicity category, my study showed that the Black ethnic group were 20% more likely to be non-adherent to their OET medication regimen than White and Asian patients. These results were consistent with other breast cancer studies focused on older women populations (Haskins et al., 2019; Yussof et al., 2022). Some other breast cancer studies found that not being White was a factor of OET-NA rather than identifying it as a problem specifically in the Black ethnicity population (Sheppard et al., 2019). This is not surprising information, since the disparity of breast cancer medication adherence among Black patients compared with White patients in the U.S. is a well-known statistic (Reeder-Hayes et al., 2021). Furthermore, many medication-NA studies with chronic disease populations identified not being White as a determinant (Chen et al., 2009; Molnar et al., 2016).

Concerning psychological symptoms and diseases, all previous studies explained both anxiety and depression as determinants of non-adherence (Mathes et al., 2014; Yussof et al. 2022); however, my study found that depression is a stronger factor than anxiety, specifically for older women with breast cancer. Also, many previous researchers did not extend their studies into psychological diseases, such ADHD, and bipolar disorders. In my findings, ADHD and bipolar disorders were determinants for OET-NA, but this issue is a less studied area in breast cancer and chronic disease populations. Still, there are some breast cancer studies that support bipolar disorders being an OET-NA factor (Haskins et al., 2019). However, one breast cancer study was against bipolar disorders being a factor for OET-NA in small sample study (Bagdadi et al., 2021). While ADHD itself creates medication

adherence issues for patients, Roberts et al. (2020) found that many psychological disease problems may come from the tendency to bring along other psychological issues. For example, ADHD patients usually also have anxiety disorder and depression diagnoses, which then compound OET-NA problems, as mentioned above.

Table 5.2.

Socioeconomic-Related Discussion

Socioeconomic-Related	My Findings	Breast Cancer	Chronic Disease
Marital status	*Single (OR 1.22), Separated (OR 1.54), *Divorced (OR 1.28), Widowed (OR 1.12)	Single, Divorced, Widowed	Non-married or no cohabitation status
Lifestyle Factor	*Alcohol use (OR 1.67), Opioid drug use (OR 1.85), *Tobacco use (OR 1.48)	Smoker (vs never smoked)5	Alcohol and drug use

Socioeconomic-related factors included marital status, lifestyle status, and living status, which is in line with previous studies (Bright & Stanton, 2018; Mohamed & Elamin, 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Xu & Wang, 2019). My findings confirmed that patients who are not married and have lifestyles that involve drugs, alcohol and/or tobacco use have an increased risk of OET-NA, which is already known from previous studies with small sample sizes for breast cancer and chronic diseases (Gast & Mathes, 2019; Molnar et al., 2016; Seng et al., 2020; Yussof et al. 2022).

I found that married patients had better OET adherence than non-married (single, separated, divorced, and widowed) patients. Most medication-NA literature suggests that the support of a spouse encourages medication adherence through the social support that they provide (Addidja et al., 2018; Chen et al., 2018; Crawshaw et al., 2016; Hansen et al., 2015;

Mathes et al., 2014). These findings can be related back to psychological symptoms in the patient-related factor analysis. For example, Xu and Wang (2019) mentioned that there is an increase in depression and anxiety among divorced breast cancer patients (which compounds the lack of spousal support). Moreover, recent systematic reviews showed that medication-NA is highly associated with the non-married group in chronic disease (Chen et al., 2023).

Concerning lifestyle factors, all patients with lifestyles that included alcohol, drug and tobacco use showed higher rates of OET-NA in the patient-related factor analysis. Also, I confirmed that using alcohol and tobacco are strongly related to OET-NA and these findings were confirmed again in my post-hoc analysis. Interestingly, previous studies were more focused on tobacco usage (smoking status) rather than other types of lifestyle factors (Sella et al., 2019). Also, there was an association between psychological symptoms (e.g., anxiety and depression) and using drug, alcohol, and tobacco (Gellad et al., 2011). Gellad's (2011) research team also demonstrated that these lifestyle factors and psychological symptoms are affecting OET-NA more strongly than not having these issues.

Unlike the other socioeconomic-related factors, living in a rural or urban area had no impact on a patient's OET-NA from univariate analysis. Even the multivariate analysis did not show any statistically significant data to make any conclusions about the effect of living status on OET-NA. Fewer studies were conducted on identifying living status, but some recent review studies suggested that there is an association between living in rural areas and medication-NA in chronic diseases (Chen et al., 2023). Another study discussed that living in a rural area might increase medication-NA due to healthcare facilities not being easily accessible (Rahmawati & Bajorek, 2018). These findings may be discovered and supported

when we work on different types of analysis in the future; for this study, the "living in rural area" sample size was too small to work with in my bigger analysis.

Table 5.3.

Therapy-Related Discussion

Therapy-Related	My Findings	Breast Cancer	Chronic Disease
Drug therapy problems	Having 4th drug therapy problems (OR 2.94)	Drug taking behavior/ attitude	Drug taking behavior/ attitude
Lifestyle Factor	*OET prescribed medication is switched (OR 2.65)	Switching medications	Switching medications (Only found in Cancer)
Therapy Types and Combinations	Radiation before Surgery (OR 2.00) (Reference: no radiation and/or surgery) No systemic & surgical therapy (OR 1.14) Systemic therapy before surgery (OR 1.19) (Reference: having systemic therapy after surgery)	(Without specific sequence) No surgery therapy1 No radiation therapy1 No systemic chemo therapy1	-

My analysis of therapy-related factors showed the effects of changes in prescribed medication, different therapy types utilized by patients, and the number of drug therapy problems experienced by a patient on OET-NA, which is in line with previous studies (Adidja et al., 2019; Chew et al., 2009; Dashputre et al., 2020; Mathes et al., 2014a, Molnar et al., 2016; Murphy et al., 2012; Sabaté, 2003; Yussof et al., 2022).

Out of all possible medication regimens and/or therapy combinations, I found that changing a patient's prescribed medication during a regimen had the greatest impact on

OET-NA. I confirmed that switching medications was still the most critical variable in my post-hoc analysis. Many previous studies recognized this increased non-adherence risk factor, but they were only focused on either breast cancer or other cancer medications (Fernandez-Lazaro et al., 2019; Yussof et al., 2022). This switching of OET medications is frequently caused by a patient's desire to avoid side effects of their current OET medication; these side effects might have already been impacting medication adherence. Several articles discussed that medication side effects are determinants in cancer patients (Noens et al., 2009) and other chronic diseases (Adidja et al. (2018; Chew et al., 2009). Interestingly, these side effects can also lead to drug therapy problems.

In terms of drug therapy problems, I have found that patients with an increased number of DTP were likely to be in the OET-NA group compared to those not having DTP issues. Again, DTP indicates that a patient had drug therapy resolution interventions, and this can be initiated by healthcare providers or pharmacists when they were concerned about the patient's medication taking behavior (Westberg et al., 2017). Many previous studies discussed patients' attitudes by considering their past drug management/therapy problems-adherence (Finitsis et al., 2019; Lambert et al., 2018; Moon et al., 2017; Paranjpe et al., 2019; Peh et al., 2021). They found that having more drug problems in the past is associated with medication-NA in chronic diseases, indicating past behaviors may impact patients' future medication adherence issues in other circumstances as well. Often these past drug therapy problems were related to a patient's medication taking behavior, even if it started from the side-effects of medications (MacDonald et al., 2018). Several articles also discussed patients' attitudes due to past drug therapy and categorized it into the patient-related factor (Chen et al., 2018; Crawshaw et al., 2016; Mathes et al., 2014). However, this is a less studied area

and previous studies have used fewer objective measures, leading to a lack of evidence to support these conclusions. In my analysis, these DTP data were statistically significant, especially in multivariate analysis with the other therapy factors (See Figure 4.13). Other factors may have been attenuated with the other therapy-related variables when it all comes together in a big analysis. However, the odd ratio error bar is quite large and due to a small number of sample sizes, this result cannot be concluded. This means that we need to study more about this variable in the future in detail. Still, my finding is beneficial to increase more evidence about therapy-related factor in older women with breast cancer populations.

Lastly, different types of therapy are reported in older women with breast cancer populations. My study results identified that patients who had radiation before surgery are 100% more likely to be OET-NA compared to those who did not have radiation and/or surgery. This result indicates that patients who had radiation tend to be more non-adherent due to radiation side effects. For example, side effects of radiation such as extreme fatigue might make it more difficult for women who are starting their OET medication to be adherent (Dhruva et al., 2010). Also, my result found that patients who did not have systemic chemotherapy and/or surgical therapy had 14 % more OET-NA compared to patients who had systemic chemotherapy after surgery. Similarly, patients who had systemic chemotherapy before surgery were 19% more likely to be non-adherent to their OET medications compared to patients who had systemic chemotherapy after surgery. These results suggest that the combination/sequencing of systemic chemotherapy with other therapies can be less critical than the inclusion and timing of radiation therapy when it comes to OET-NA; this is important for patients considering this form of treatment. There are fewer studies that are focused on specific sequences of these types of therapy, so my finding can be

useful to understand older breast cancer populations. Previous studies were more focused on either having specific therapy or not, rather than combining it with different therapy sequences (Yussof et al., 2022).

Table 5.4.

Condition-Related Discussion

Condition-Related	My Findings	Breast Cancer	Chronic Disease
Disease Characteristic	*Stage II (OR 1.10) Stage IV (OR 1.38) (reference: Stage I)	Stage IV, Earlier stage (I or II)	-
Comorbidity	AMI (OR 1.38), PVD (OR 1.19), *Obesity (OR 1.10), Migraine (OR 1.20), Liver disease (OR 1.12), No HTN (OR 1.08), No HLD (OR 1.09), Fibromyalgia (OR 1.20), Epilepsy (OR 1.52), Diabetes (OR 1.08), COPD (OR 1.20), CHF (OR 1.13), Anemia (OR 1.15), Hip Fracture (OR 2.21), Ulcers (OR 1.44)	Overweight or obese No HTN Cardiopulmonary comorbidities	CVD-risk (CAD, HTN, diabetes, and HLD)

Abbreviations are acute myocardial infarction (AMI) hyperlipidemia (HLD) hypertension (HTN), human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS), coronary artery disease (CAD), congested heart failure (CHF), cardiovasicular disease (CVD), peripheral vascular disease (PVD)

Condition-related factors included disease characteristics and comorbidity factors. Comorbidities were all positively related with medication-NA in any chronic disease population throughout all the studies (Bosco-Levy et al., 2016; Farias et al., 2018b; Hagen et al., 2019; Halli-Tierney et al., 2019; Tan et al., 2021; Ma et al., 2020; Peh et al., 2021; Pranjpe et al., 2019; Sabaté, 2003; Wulaningsih et al., 2018; Yussof et al., 2022).

Concerning disease characteristics, I investigated patient's cancer stage. From my analysis, I found that patients with Stage II and Stage IV cancer were more likely to be non-

adherent than Stage I. Stage III cancer was not statistically significantly correlated with OET-NA, but individuals in Stage II were less likely to be OET-NA when compared to individuals in Stage I of their cancer. I compared these results with previous studies with divided trends of OET-NA; Stage II and IV are both stronger OET-NA determinants for older women with breast cancer populations (Haskins et al., 2019; Hagen et al., 2022; Wang & Du, 2015; Wulaningsih et al., 2018; Yussof et al., 2022).

When it comes to comorbidity factors, almost all comorbidities were a risk factor for OET-NA; however, obesity was a significant determinant of OET-NA in both comorbidity category analysis (Table 4.17) and post-hoc analysis (Table 4.21). In comorbidity analysis, hip-fractures had by far the worst rates of non-adherence. Patients with hip fractures were twice as likely to be non-adherent. Also, the cardiovascular, and cardiopulmonary disease groups were recognized as having a risk factor (e.g., AMI, CHF, COPD, and PVD). Specifically, about 40% of AMI patients were more likely to be non-adherent than patients without this condition. Interestingly, patients who did not have hypertension or hyperlipidemia were more likely to be non-adherent than those experiencing those symptoms. This result may be affected by the fact that the majority of breast cancer patients (more than 60%) have hypertensions and hyperlipidemia. All other comorbidities showed only a 10-30% increase in a patient's likelihood of non-adherence.

These comorbidity results corresponded with several breast cancer studies focused on comorbidity factors such as having obesity, and cardiopulmonary disease risk (Yussof et al., 2022), and no hypertension (Sella et al., 2020). Furthermore, several previous studies emphasized that cardiovascular disease (CVD), diabetes, and hyperlipidemia are common comorbidities, and these are common comorbidities for cancer patients as well (Cho et al.,

2018; Zullig et al., 2022). Specifically, cancer patients with CVD or CVD risk factor-related comorbidities (i.e., diabetes, hypertension, and hyperlipidemia) had an increase medication-NA in general (Zullig et al., 2022). Specifically for breast cancer patients, osteoporosis is counted as another important comorbidity since OET increases risk of bone loss and exacerbates osteoporosis (Perez et al., 2006). Our data did not show associations on OET-NA with osteoporosis or hyperlipidemia, but CVD related factors were recognized as a strong determinant. Several previous literatures discussed that CVD risk is related with OET-NA due to alteration of gynecological effects with it (Lacrossi et al., 2018; Ma et al., 2021, Meneveau et al., 2020; Yussof et al., 2022).

Table 5.5.

Healthcare Team/System -Related Discussion

Healthcare team/system - Related	My Findings	Breast Cancer	Chronic Disease
Healthcare team characteristics	*Institution provider (shares patients) (OR 1.54) (reference: solo practitioner)	-	Increased complexity in the provider team (only found in Cancer study)
Healthcare system characteristics	Subject to deductible (OR 1.25), Coinsurance $20-40 (OR 1.31), Coinsurance $20-40 (OR 1.17) (Reference: having no coinsurance payments group variables, and not subject to deductible)	Increased out-of-pocket	Insurance types, increased coinsurance, copayments, deductibles or caps

Health care team/system-related factors included CMR provider types, provider partnership status, and co-insurance amount with deductible status. Two factors are consistently recognized as important health care team factors in chronic diseases: (a) the

historical amount of patient sharing among providers and (b) prescribing provider's practice area or medication reviewing healthcare professionals (Bosco-Levy et al., 2016; Guedes et al., 2017; Ma et al., 2020; Moon et al., 2017; Lambert -Côté et al., 2020; Lin et al., 2017; Peh et al., 2021; Paranjpe et al., 2019; Sabaté, 2003; Trabulsi et al., 2014).

In terms of healthcare team characteristics, I have found that patients having multiple providers can increase the risk of OET-NA. This understudied risk factor may be due to the increased communication required between providers when many are involved in a patient's care (Lambert-Kerzner et al., 2015; Marques & Pierin, 2008). For example, some studies discovered that patients with chronic diseases feel unable to discuss their medication concerns with healthcare providers due to a limited trust-based patient-provider communication relationship and the same trends were also recognized in cancer studies (Lin et al., 2017; Moon et al., 2017). These lower levels of trust between patient and provider may come from the fact that patients are not consistently interacting with the same provider and therefore cannot build a stable relationship. While this is a very important issue, it remains understudied because of the difficulty of observing patient-provider relationships, leading to limited sample sizes and incoherent research designs that use subjective measures. Also, there was an insignificant statistical result that when physician review medication, patients are likely to be OET-NA compared to when nurses and nurse practitioners review patient's medications. It is important to continue investigate these correlations in the future, since several literatures discussed that nurses tend to provide more effective educations than other professions including medication educations (Hesshmati Nabavi et al., 2016).

Concerning healthcare system characteristics, my results indicated that Medicare insurance is associated with OET-NA; this was found in other breast cancer and chronic

disease studies as well (Mathes et al., 2014b). My study concurs with existing studies, but increases generalizability due to larger sample sizes Also, there were trends that patients with lower amounts of co-insurance or those who were subject to meet deductibles are more likely to be OET-NA compared to patients who have no coinsurance or their payment was covered by Medicare after deductible. Coinsurance is defined as a percentage of the cost that a patient needs to pay (Schmidt & Hogan, 2000). Some studies suggested that patients were likely to have secondary insurance coverage, such as other private insurance, when their coinsurance payments were higher than usual amount (Schmidt & Hogan, 2000). Unfortunately, I did not have secondary insurance information in the Medicare dataset, but these results suggested that patients who have lower coinsurance may not have secondary insurance. These patients may struggle to pay their bills out of pocket, and this can eventually increase their risk of OET-NA, as our data shows. Moreover, Mathes (2014b) found that higher co-payments with Medicare or private insurance always positively impacts medication-NA in chronic disease (Bosco-Levy et al., 2016; Ma et al., 2020; Yussof et al., 2022). The data collected on CMR provider types did not show any statically significant results, making it difficult to have any conclusions about this factor's effect on OET-NA. Sample sizes were too small (e.g., 151 Nurse practitioners, 15 Physicians, 14 pharmacists) to conclude the relationship between CMR provider's characteristics and patients' OET-NA. Provider partnership status analyzed the way patients being seen by multiple providers (e.g., multiple providers working in the same group clinic or institution) effected the likelihood of OET-NA. I found a positive correlation between instances where a patient does not consistently receive care from the same provider and OET-NA. Moreover, OET-NA patients were likely to be qualified for the deductible before Medicare starts helping to pay their bills. Finally, no statistically

significant data were found concerning co-insurance-related variables based on information from the NCH database. This indicates that even these results of health care system may impact on OET-NA; however, we cannot conclude this in my study. Previous study has found some positive relationship with these factors; however, all the studies utilized less than 1,000 samples to investigate this problem (Dashputre et al., 2020; Lafeuille et al., 2014; Sheppard et al., 2019; Tang et al., 2018).

My post-hoc analysis result confirmed the same trends of finding from univariate and small group of multivariate analysis. I found obesity, Stage II, Black ethnic group, alcohol or tobacco users, non-married status, switched OET medications, having multiple providers, and depressions to be determinants of OET-NA. Interestingly, obesity, Stage II cancer, and being in the Black ethnic group remained the strongest factors of OET-NA, in keeping with prior analyses. However, some other factors were stronger determinants of OET-NA in conjunction with each other than alone, even when the followed the same trends as previous analyses. For example, while non-married status is a known factor of OET-NA, patients who were single or divorced were more likely to be OET-NA when looking at all factors together than those who were widowed or separated. I have also found that if the univariate of variables were not statistically significant due to small sample sizes, post-hoc analysis showed the same results on those small sample variables. For example, American Indian/Alaskan Natives group (0.32%) and living in the rural areas (1.06%) in the category of race and living status respectively. It is valuable to understand the data characteristics in one category; however, we cannot ignore the variance and other confounder effects when we analyze together amongst larger groups of other categorical data (Pourhoseingholi et al., 2012). In terms of fitting, pseudo-R squared was 0.023, which indicates that it may have

more variance in the independent variable associated with the dependent variables (IBM, n.d.). Small sample sizes of the American Indian/Alaskan Natives group (0.32%) and living in the rural areas (1.06%) in the category cause this big variance on certain variables. Many clinical studies likely to have low pseudo-R squared such as 0.02 value because the focus of the result is identifying significant relationship ($p<0.05$) rather than providing better prediction in this case by using logistic regression (Desai et al., 2018; Grace-Martin, 2019). Even though some categories had small sample sizes compared to others, it is critical to include those data into our study as long as it had statistically significant results (i.e., therapy-related and healthcare team/system-related determinants), since these factors were less studied compared to other factors in previous literature. From this reason, we cannot generalize this result.

Surprising facts that I have found from this study were that switching OET medications consistently were shown as a strong factor of OET-NA. Also, many patient-related factors are more strongly linked back with condition-related problems in older women with breast cancer. For example, mobility issues were significantly related to certain comorbidities such as ulcers. This suggests that it is beneficial to perform a future network analytics study which can explain the strength and flow of interrelationships between variables. It was also confirmed that previous studies' trends of OET-NA were valid, and that new factors were discovered (i.e., Bipolar disorder, ADHD, hearing impairments, and mobility impairments, alcohol use and opioid drug use, multiple providers, comorbidities).

Strengths

A strength of my study is that I used both the MPR and the PDC methods, unlike many other studies that used just the MPR method to calculate medication adherence rates.

This PDC method compensates for the several issues that come with only using the MPR method and it is a newer method to calculate medication adherence rates. Furthermore, the PDC method provides more accurate adherence rates than the MPR method by reducing errors that were often shown as over-adherence in the MPR method by adding all up the overlapped prescription dates as extra dates of adherence. Since many previous older studies (published before 2015) utilized the MPR method most frequently, it benefited my study to compare results of OET-NA rates in the last ten years. I confirmed that the MPR methods created over-adherence of OET, which corresponds that many breast cancer patients were likely to pick their medications up earlier than suggested dates.

Moreover, our study results were more generalizable since it matches with national breast cancer samples. For example, national data of breast cancer ethnicity were 60.43% Non-Hispanic White, 13.70 % Non-Hispanic African American, 6.70% Non-Hispanic Asian and Pacific Islander and 18.33% as Hispanics (CDC, 2020). Our sample's ethnicity was 82.62% White, 11.06 % African American, 5.97% Asian or Pacific Islander, and 0.35% American Indian/Alaska Native. Considering Hispanics into White group, as many previous studies showed that Hispanic mostly identify them as White (Liu, 2014), national data of White would become 79%, which is very similar as our sample of percentage. Other ethnic groups percentages are very similar as national data.

Previously, the biggest sample sizes were identified as less than 20,000 patients in my literature review in Chapter 2. This is critical research since no other studies worked on big data analysis to understand OET-NA phenomena as a comprehensive study.

Lastly, this study utilized binary logistic statistical regression to analyze OR via Python computing programs with MongoDB. This regression modeling was able to compute

big data quickly by using flexible databases, which is a NoSQL system. The SQL is created in the 1970's to optimize storage and stability but has a too rigid structure that needs high maintenance for expertise; however, NoSQL databases have developed in flexible structures around 2000 to allow different types of data models, scale horizontally, and have incredibly fast queries (Ali et al., 2019). No previous studies worked on this OET-NA analysis in the nursing science field utilizing these powerful tools to understand big data collections.

Limitations

Several limitations were noted in this study. First, the results may not be generalized to other patients or those not enrolled in Medicare Part D. According to the Department of Health and Human Services in USA (2022), 74% of 63 million Medicare beneficiaries enrolled in Medicare Part D in 2019. This is still a very large number compared to other previous studies. Second, some missing data may increase the risk of bias on multivariate analysis across the different multi-level factors. Unfortunately, some multi-level data (e.g., marriage status, therapy combinations, insurance claims directly link with prescriptions) have about 40% missing data. This missing data may increase the risk of bias to interpretate the result. To avoid any other risks of understanding this data, I utilized the Phyton program to run the completeness test of entire samples and removed any missing data to calculate the accurate information rather than making imputation from unknown data. For these reasons, I only retrieved about 35,326 patients' data for my post-hoc analysis from all multi-level systems such as patient-related, socioeconomic-related, therapy-related, condition-related and health care team/system-related level systems. Third, there could be some potential unmeasured confounders that affected the study's findings. For example, provider's specialty was found to be a significant factor affecting OET-NA from the literature review; however, it

was inconclusive due to a large number of missing linkages between Medicare Part D data and insurance claims (NCH) databases, where the provider's specialty information was saved. Also, the NCH database didn't share what type of co-insurance the patients used. Moreover, there was no information to track the patient's provider for medication prescriptions and its exact insurance claims. Unfortunately, the NCH database includes all insurance data together without the type of detail breakdown needed for my study. Fourth, this study did not include each phase of medication adherence in relation to an individual's initiation, implementation, and discontinuation. This was not included in our research question, but it can provide more information to investigate what adherence phase has the greatest OET-NA. Lastly, prescription refill data is an indirect method, and it cannot accurately capture the real-time medication administration data. One of the biggest biases of this method assumes that prescription-refilling data correspond to the patient's medication-taking behavior (Lam & Fresco, 2015). For example, this method assumes initiation phase of medication adherence from ABC taxonomy. Specifically, we do not know that when the medication is taken exactly as prescribed as long as patients are picking up their medication. This method could not discover partial NA during the prescription supply period.

Implications

Nursing Practice

There are several possible implications for nursing clinical practice related to OET-NA determinants with breast cancer. It is critical to have these results because no previous studies focused on identifying ten years of OET-NA rates, partially since it is a new recommendation of treatment. While this ten-year recommendation is not yet the standard for OET use by international guidelines, some patients are already taking the OET for up to ten

years. Our study found that about 40% of breast cancer patients in 2019 were taking OET for five to ten years. This suggests that health care professionals, including nurses, need more information to support patients' new treatment recommendation, especially since almost half of the breast cancer patients are already taking OET for more than five years.

Also, our study used most recent breast cancer patient data compared to previous studies; we focused on data from 2019, which is the most updated available from the SEER Medicare database (released early 2023). This allows nurse researchers and nurses to see the most recent trends of OET-NA in a large sample that can be applied to nursing practices. Moreover, this study allows nurse researchers and nurses to understand OET-NA determinants quickly by breaking down the information into categories so that it can easily be applied back to nursing interventions and practices. Identifying OET-NA rates and multi-level determinants of OET-NA will be the first step in developing and testing interventions to improve OET adherence in breast cancer patients, which has the potential to decrease morbidity and mortality, and increase QOL. This study identified that five categorizes of OET-NA determinants to support building more robust nursing interventions. By utilizing these known determinants, nurse researchers and nurses can utilize tailored OET-NA interventions for breast cancer patients, including patients whose treatment regimens have been extended from five to ten years.

Moreover, my statistical analysis tool can provide prediction modelling from logistic regression analysis. This prediction modeling tool can support building tailored nursing interventions by providing three to four predicted determinants when researchers enter one factor. For example, if a researcher submits that a patient is of American Indian/Alaska Native ethnic group, the prediction modeling tool might suggest that the patient may also be

living in a rural area, be diagnosed with anxiety and/or have comorbidities, specifically diabetes and/or hypertension. Therefore, it will be possible to adopt tailored nursing interventions more widely and in bigger samples quicker.

Emphasizing multi-level influences is critical for nursing research because nurses are uniquely positioned to assist patients in changing medication adherence behaviors to improve QOL and outcomes. Nurses can coach patients at each of the factor levels (patient-related, condition-related, therapy-related, socioeconomic-related, and health care team/system-related factors) to influence their behavior changes. When it comes to older woman with breast cancer specifically, nurses can promote OET adherence behavior, leading more breast cancer patients to eventually enhance their QOL and decrease recurrence rates, mortality, and medical costs.

Nursing Theory

Existing studies have commonly overlooked multi-level determinants, even though medication-NA is a complex problem that is influenced by multi-level determinants like patient-related, socio-economic-related, therapy-related, condition-related, and healthcare team/system-related factors. Specifically, no previous OET-NA studies utilized theoretical frameworks such as the WHO's FDM or Bronfenbrenner's EST. This study utilized both of these frameworks to better understand potential multi-level influences of OET-NA determinants. Bronfenbrenner's EST supported the use of FDM to enhance our understanding of OET-NA determinants. Investigating FDM factors will help nurses understand the current issue of OET-NA among breast cancer patients more clearly. The blueprint I have created of multi-level determinants can guide nurses to educate their patients on the importance of medication adherence to treat breast cancer. This blueprint can be

utilized to create tailored nursing interventions for specific vulnerable populations. These results will be especially useful to nurse researchers who create their OET-NA interventions using Bronfenbrenner's EST and/or WHO's FDM because that will build upon the existing foundation of the theoretical framework.

Nursing Policy

Two of the health care team/system subfactors analyzed in this study have meaningful implications for nursing policy. First, this study attempted to find a trend that when nurses or nurse practitioners reviewed patients' medications with them, their OET-NA rates were lower because patients are more adherent with OET when it is the nurses and/or nurse practitioners who review their medication with them as opposed to other healthcare professionals such as physicians and pharmacists (Hesshmati Nabavi et al., 2016). These finding would be critical to support nurses' efforts to education and guide patients concerning their medications. It would be beneficial to implement a nursing policy to reinforce patient education and guidance in nursing practices because it would increase adherence not only among breast cancer patients taking OET but across the board.

Second, this study found an association between fewer Medicare claims support and increased OET-NA. When reviewing the insurance claim (NCH) and medication management (PDEMTM) database, I found there was no specific field or variable where nurses, or other healthcare professionals, could record or confirm to support patients' insurance claims in any form. It would be beneficial if nursing policy could allow for nurses to access and document insurance claim issues for non-adherent patients so that they could identify potential determinants for medication-NA. Sometimes, breast cancer patients are struggling to pay for medication or have other concerns that involve insurance that led them

to be non-adherent. If nurses could work with these patients to fill out claims and answer questions, there would be an increase in OET adherence.

Future Research

First, I would like to have an ethnic group focused study to pinpoint links between Black ethnic group patients and other determinants for OET-NA. This is important information to discover; however, there was no clear previous study research about this topic in a large sample. Second, if in the future, the SEER Medicare team would be interested in linking the two sets of database information together, I would use that new dataset to do a trajectory analysis of medication adherences and create more conclusive data. Third, I would like to apply the statistical physics network analytic tool to see the interactions between all of the determinants. I wish to find why several determinants were more strongly related than others and how they interact in order to cause higher rates of OET-NA (i.e., divorce with psychological symptoms, which is known in previous small size sample study (Xu & Wang, 2019). Fourth, I would like to conduct a more detailed medication adherence study in relation to the effects of individuals' initiation, implementation, and discontinuation of medication-NA. I want to work on finding determinants with these different types of adherences. Lastly, I would like to apply our study to ten years' or more worth of medication adherence data and compare the results concerning the determinants identified in this study since this study focused on the most recent year of OET-NA determinants.

Conclusions

The OET-NA rates in 2019 SEER Medicare database was 6.35% among breast cancer populations. The study found that ethnicity, marital status, lifestyle (using drug and tobacco), changed prescribed medication, having psychological symptoms and diseases, having cognitive issues, having comorbidities, having more drug therapy problems, and having insurance issues significantly affected OET-NA among breast cancer patients, which aligned with my Chapter 2: Literature Review. My result confirmed previous literature that has conducted studies with small sample sizes among breast cancer patients. These results were more generalizable than previous studies since this study used much larger samples. My study confirmed that breast cancer patient's medication-NA determinants were different than other chronic disease. This indicates that it is critical to investigate different factors on specific diseases and have tailored nursing interventions to increase medication adherence. This study is critical since it also suggests that we can expand this study to build a program to have predicting modeling analysis for tailored nursing intervention on specific keywords. Future studies will confirm how strongly these determinants were linked and related to each other to provide better information about OET-NA factors depending on their medication adherence phase.

APPENDIX

APPENDIX A: Literature Review Articles

Matrix 1: Medication Adherence in Chronic Disease (20 articles)

Author/Year/ Design	**Sample/ Setting**	**Instruments/ Methods**	**Results**	**Key Findings**
Adidja et al. (2018) • **Design:** cross-sectional	• N=183 hypertensive patients (Mean age = 60 years old, Female 65%) • Cameroon	• Adherence measure: Morisky medication adherence scale • Focused on patient, therapy and socioeconomic-related factors • No theory utilized	• Non-adherence rate: 66.6% • Forgetfulness, multiple daily doses, lack of finances, and side effects of drugs were associated with non-adherence.	• Factors related with non-adherence: financial constraints, medication side effects
Al-Noumani et al. (2016) • **Design:** cross-sectional	• N= 45 hypertensive patients (Mean age=52, Female 64%) • Oman	• Adherence measure: Morisky medication adherence scale • Other measure: Beliefs about Medicines Questionnaire, Brief Illness Perception Questionnaire and the revised Medication Adherence Self-Efficacy Scale • Focused on patient-related factors (health belief such as effectiveness, concerns of medication, self-efficacy) • Utilized the common-sense self-regulation model	• Non-adherence rate: about 50% of antihypertensive medicine.	Higher self-efficacy and stronger health beliefs regarding medication necessity were significantly related to adherence

Bane et al. (2006) • **Design:** cross-sectional	• N= 139 hypertensive patients (Mean age=52, Female 50%) • Northern Ireland	• Adherence measure: some data (n= 40) from past medication records in the Belfast City Hospital between June 2000 to October 2001, other data (n=99) from Morisky medication adherence scale • Other measure: Self-efficacy scale, Theory of Planned Behavior questionnaire • Focused on patient-related factors • Self-efficacy Theory of planned behavior	• Non-adherence rate: 20.9% (n = 29) (Definition of non-adherence: patients are taking of medication less than 80% in recommended regimens) • Adherence was related to intentions (the effect size, b = 0.54) and by the measure of subjective norms (b = 0.19), which is the person's perception of social pressure from significant others to perform the behavior.	• Adherent patients have higher levels of self-efficacy • Experiencing symptoms (headaches, dizziness) of hypertension are positively associated with adherent with their prescribed medication
Broekmans et al. (2008) • **Design:** systematic review (quantitative studies)	• N= 14 articles of adult patients with chronic non-malignant pain and taking prescribed pain medication, all published before 2006.	• Adherence measure: self-report, questionnaires, MEMS, pill count, refill data, urine screening.	• Pain intensity (measured with a numeric rating scale), pain duration and educational level did not correlate with adherence (Berndt et al., 1993). • The pain medication non-adherence ranges from 7.7% to 52.9%.	• Factors related with non-adherence: younger age, duration of disease, male gender, different medications
Cedillo-Couvert et al. (2018) • **Design:** Prospective observational	• N=3,305 chronic kidney disease patients from 2003 to 2008 (Mean age=59, Female 45%) in the USA (multicenter)	• Adherence measure: Self-reported medication adherence • 3 items as high, medium (only forgetting a pill at least 1 day in the past week were categorized), low adherence. (Purposefully adding or missing a pill 1 day or more in the past week) • No theory utilized	• 32% of the patients were non-adherent • Strong association between intentional nonadherence and adverse outcomes. • Low medication adherence is an underrecognized but important risk factor for CKD progression.	• Factors related with non-adherence: greater comorbidity burden, racial/ethnic minorities

Chen et al. (2009) • **Design:** cross-sectional	• N=277 Taiwanese hypertensive patients (Mean age=66, Female 40%)	• Adherence measure: The Medication Adherence Inventory • Other measure: Illness perception questionnaire • Focused on patient-related factors	• 17.7% of the patients were non-adherent (taking less than 80% of their antihypertensive medications).	• Symptoms experienced after a hypertension diagnosis, symptoms for blood pressure prediction, personal control, balance and cultural causal attribution were significant predictors of adherence to self-management
Chew et al. (2015) • **Design:** cross-sectional	• N=700 Malaysian type 2 diabetes patients (Age older 60=26.1%, Age 51-60= 39%, Age younger then 50 = 26.1%, Female 52.8%)	• Adherence measure: Morisky medication adherence scale • Other measure: Diabetes Distress Scale, The World Health Organization Quality of Life-Brief score, Patient Health Questionnaire	• 43.53% of the patients were non-adherent (MMAS <6) • Older patients (over 60) were more non-adherent than younger patients. • most of the patients were non-smokers and undertook some exercise; about 80% reported having hypertension but antihypertensive usage was almost 90%	• Factors related with non-adherence: being a younger adult with T2D, higher income, and depressive symptoms were significant independent determinants
Colbert et al. (2013) • **Design:** cross-sectional, retrospective secondary data analysis	• N= 302 (Mean age=68, Female 63%) African American and White American HIV/AIDS patients (Mean age=52, Female 56%)	• Adherence measure: data from electronic event monitoring from January 2004-December 2007 in clinical study (2R01NR04749), Self-Efficacy Beliefs subscale of the HIV Self-Efficacy Scale for Medication Taking (Cronbach's alpha of 0.95) (Erlen et al. 2010).	•The mean adherence based on electronic event monitoring was 67.71 %. •About 80% (n=241) of participants are recorded as non-adherent (HIV studies generally considers cut-off point is 95% or higher)	• Higher medication-taking self- efficacy was associated with higher medication adherence; however, functional health literacy was not significantly related to either medication

	• Western Pennsylvania and eastern Ohio, U. S. A	• Focused on patient and socioeconomic-related factors • Social Cognitive Theory		adherence or self-efficacy beliefs.
Crawshaw et al. (2016) • **Design:** systematic review & meta-analysis	• N= 17 articles, adult patients (> 18 years old) after acute coronary syndrome (myocardial infarction and/or unstable angina) between 2000 and 2014 • USA (n=9), Europe (n=6), Israel (n=1), China (n=1), Argentina & Brazil (n=1)	• Adherence measure: self-report, questionnaires (Brief Medication Questionnaire, MMAS, MEMS (80% cutoff), medication adherence report scale, and medical outcome study specific adherence scale).	• 8 out of 10 studies found an association between depression and non-adherence. • A meta-analysis result showed that depressed patients were twice as likely to be non-adherent compared to patients without depression. • 3 out of 3 studies reported that treatment medication beliefs-related, and social support were associated with better adherence. • Insufficient data for meta-analyses .	• Factors related with non-adherence: Cognitive-related factors (i.e., Beliefs, perceptions, and attitudes) towards cardiac treatment, mood-related factors (i.e., depression, comorbidities with psychosocial symptoms, and social support
Dennis et al. (2011) • **Design:** cross-sectional	• N =608 Urban Indian hypertensive patients (Mean age=58, Female 49%)	• Adherence measure: Brief Medication Questionnaire • Focused on patient and socioeconomic-related factors • No theory utilized	• About 50% of patients were non-adherent. • Non-adherent factors: Belief barrier (39.14%), access barrier (82.57%), recall barrier (62.17%), financial related reasons (54.93%)	• Finical reasons and recall barriers (i.e., forgetfulness) are most cited factors without considering rural and demographic backgrounds in hypertension management

Fernandez-Lazaro et al. (2019) • **Design:** cross-sectional	• N =299 adult patients with chronic condition(s) who are prescribed medication in primary healthcare centers of Spain (Mean age=66, Female =48.5%)	• Adherence measure: Morisky-Green-Levine questionnaire • Focused on patient, socioeconomic, healthcare team and healthcare system-related factors • WHO's multi-dimensional model (FDM)	• 44.5% of participants were non-adherent • Patient-related (functional indecency using the Barthel index, the use of aids such as reminders, knowledge of medications, quality of life), socioeconomical-related (gender, age, immigration status, income, living alone, education level), condition-related (# of chronic conditions, adjusted morbidity group, lifestyle behavior such as alcohol, tobacco use, levels of physical activity), therapy-related (# of prescriptions, pills, injection use, inhaler use), healthcare team and system-related (frequency of follow up, patient-provider communication, perceived quality of healthcare delivery, educational pamphlets were received) related factors	• Factors related with non-adherence: younger age (mean age 62) than older age (mean age 69), higher number of pharmacies used for medication refills, less having treatment information, less having adequate knowledge about medication regimen, and less self-perception of a good quality of life
Gast & Mathes (2019) • **Design:** systematic review	• N =21 systematic reviews which include adult patients (≥16 years) with chronic disease	• Adherence measure: direct (level in the blood) and indirect (self-report, PDC, MEMS, pill count, MPR) measures.	• Higher education, employment, higher financial status and marriage/partnership mostly showed a positive effect on adherence, the impact was unclear because of the high uncertainty of the underlying evidence	• Factors related with non-adherence: less socioeconomic status, less social support, an ethnic minority, depressions, Co-payments (any or higher)

			• Therapy-related factors (e.g., intake regime) and disease-related factors (e.g., duration) mostly showed no impact on adherence. • Analysis of gender showed inconsistent. • Impacts of other mental and physical comorbidities were uncertain. • The impacts of medication costs and insurance status were uncertain	
Hansen et al. (2015) • **Design:** retrospective secondary data analysis	• N =7,933 cardiometabolic conditioned U.S. veterans (including diabetes, hypertension, dyslipidemia, and heart failure) from 2008 to 2010 (Mean age=66, Female =48.5%)	• Adherence measure: veteran administrative claim data using continuous multiple-interval gap (non-adherence was defined as a gap ≥20% or, refill adherence >80%) • The number of cardiometabolic conditions at baseline was a sum of the 4 conditions examined (hypertension, diabetes, dyslipidemia, and heart failure). • No theory utilized	• The measured tools of administrative claims–based continuous multiple-interval gap was effective with identifying adherence tendency. • The refill adherence improved with the number of cardiometabolic conditions.	• Patient's cardiometabolic conditions may not be a significant factor of medication adherence. • Number of prescribers were not significant predictors of refill adherence in this study.
Hiko et al. (2012)	• N =9 articles include adults living with HIV/AIDS	• Meta-analysis was conducted using fixed and random effects model with mantel Haenszel method.	• White adults were 1.38 times more likely to non-adherent when compared with black adults living with HIV/ AIDS.	• Factors related with non-adherence: Being White, Non-depressed, using

• **Design:** systematic review and meta analysis (prospective & retrospective studies, case-control and comparative cross-sectional studies)	(aged ≥18 years) who receiving antiretroviral therapy between 1997 to 2011 • USA, Dominican republic, Ethiopia, Bostswana, India, Kenya, Switzerland, Spain	• Studies identifying determinants of non-compliance regarding antiretroviral therapy (socioeconomic-related, health service-related, psychosocial- and behavioral-related and clinical-related outcome measures)	• Non-depressed adults were 1.77 times more likely to non-adherent when compared with depressed adults living with HIV/AIDS. • Substance non-user were 2.04 times more likely to non-comply when compared with substance user adults living with HIV/ AIDS	substances, and higher CD4 counts
Hussein et al. (2020) • **Design:** cross-sectional, retrospective secondary data analysis	• N =2,420 hypertensive patients from the outpatient cardiac clinics in Egypt (Age older 65=66.7%, Age 40-65= 45.6%, Age younger then 40 = 14.3%, Female= 66.7%)	• Adherence measure: Modified Morisky medication adherence scale • Other measures: data from past medication records between September 2015 to September 2019 • Focused on patient and socioeconomic-related factors • No theory utilized	• 53.88% of participants were non-adherent • In the elderly, fewer patients were adherent to take medications (67.4% non-adherent for adults older than 65).	• Factors related with non-adherence: Illiterate patients (low education level), low income, # of comorbidities, polypharmacy, and living in rural area.
Krueger et al. (2015) • **Design:** systematic review (all	• N =17 articles which include adult patients with chronic heart failure in Asia, Australia, Europe,	• Adherence measure: direct (serum digoxin concentration) and indirect (self-report, PDC, MEMS, pill count, MPR) measures (cutoff ≥75% (n=3), or ≥80% (n=4)).	• 7 studies: statistically significant relationship between age and medication adherence. • 6 studies: increased age is correlated with higher medication adherence	• Factors related with non-adherence: younger age

quantitative studies)	USA, and West-Africa		• 1 study: age range of 57 to 64 years are affected by non-adherence to angiotensin-converting enzyme inhibitors. • 10 studies: no significant relationship.	
Mannan et al. (2020) • **Design:** cross-sectional	• N =2,061 type 2 diabetic patients in Bangladesh (Mean age = 50.6, Female= 40.2%)	• Adherence measure: Morisky medication adherence scale • Other measures: data from past medical histories • Focused on patient and socioeconomic-related factors • No theory utilized	• 53.7% of participants were non-adherent • Personal medical history data: co-morbidities (hypertension, heart diseases, eye diseases, kidney diseases, neurological diseases, diabetic ulcer, cancer, asthma, TB), Fasting blood sugar, body mass index, behavioral characteristics (tobacco use, consumption of fruits and vegetables)	• Factors related with non-adherence: male gender, less family income, diabetic ulcers, and lower consumption of fruits and vegetables (less than 3 times a day).
Mathes et al. (2014) • **Design:** systematic review	• N = 9 studies including adult patients with hepatitis C who are taking ribavirin (prospective and retrospective cohort studies, cross-sectional studies) in the U.S.A., Europe, and Japan.	• Adherence measure: self-report (questionnaires such as Morisky scale, VAS, BMQ), MEMS, pill count	• No general conclusions were made due to the heterogeneity (e.g., patient characteristics, regimes, settings, countries). • Alcohol consumption, education, employment status, ethnic group, and weight showed no effect on adherence.	• Factors related with non-adherence: psychiatric disorders (n=5), higher dose of medication (n=3), comorbidity (HIV (n=2), hemoglobin level (n=2)), being female patient (n=6),
Molnar et al. (2016)	• N =32,348 U.S. veterans who	• Adherence measure: cardiovascular drugs data from database (US Renal	• Patients with MPR less than 80% (non-adherent group) had	• Similar trends in PDC, MPR and non-

• **Design:** Secondary data-analysis	transitioned to dialysis during 2007–2011 (Mean age = 72, Female= 4%)	Data System, Medicare, US department of Veteran Affairs pharmacy dispensation record) records using proportion of days covered (PDC) and persistence during the pre-dialysis year. • Persistence was coded as being 1 (present) if a patient refilled each subsequent prescription with gaps not exceeding 60 days; otherwise, it was coded as 0 (absent, or non-persistent).	significantly higher risk for all-cause mortality. • Comorbidity list (Charlson comorbidity index, diabetes, cardiovascular/ cerebro-vascular diseases, myocardial Infarction, congestive heart failure, peripheral vascular disease, hypertension, cerebrovascular diseases, dementia, chronic pulmonary diseases, connective tissue diseases, peptic ulcer diseases, mild liver diseases, moderate to severe liver diseases, paraplegia and hemiplegia, malignancy, metastatic carcinoma, depression, anxiety, AIDS/HIV)	persistence with mortality risk analysis • Factors related with non-adherence: younger age, not married; African American compared to White, not on cardiovascular related medications (i.e., statin, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker); less diagnosed with hypertension; high cholesterol levels, and less favorable metabolic and anemia markers • Poor pre-dialysis medication adherence and persistence in the year preceding ESRD onset are associated with increased all-cause and cardiovascular mortality.

Nonogaki et al. (2019) • **Design:** cross-sectional	• N =773 type 2 diabetic patients in Cambodia (less than 44 years old=9.2%, 45-54 =26%, 55-64=38.4%, older than 65=26.3%)	• Adherence measure: Modified Morisky medication adherence scale • Other measures: modified diabetes mellitus knowledge, attitudes, practices test • Focused on patient and socioeconomic-related factors • No theory utilized	• 53.7% of participants were non-adherent • Being female, were not married, and higher monthly family income tends to have higher medication adherence. • Scores of knowledges, attitudes, and practices had significantly higher for adherent patient group than non-adherent group	• Factors related with non-adherence: family income, diabetes mellitus-related complications, less use of health services, alcohol consumption, and following special diet.
Unni et al. (2021) • **Design:** cross-sectional	• N1 =2,983 in 2017 (Mean age = 61.6, Female= 40.6%) • N2 = 5,416 in 2018 (Mean age = 61.05, Female= 53.03 %), • N3 =5,268 in 2019 (Mean age = 60.38, Female= 47.3%) type 2 diabetic patients in the U. S. A.	• Adherence measure: Medication Adherence Reasons scale • Other measures: National Health and Wellness Survey from 2017 to 2019 • Focused on patient and socioeconomic-related factors • No theory utilized	• 24.3% of participants were non-adherent •No significant improvement in adherence with type 2 diabetic medicines over time, regardless of better awareness and extensive diabetes education	• Factors related with non-adherence: forgetfulness, not know how to take their medicines, cost, and concerns about the long-term effects of the medicines.

Matrix 2: Medication Adherence in Cancer (20 articles)

Author/Year/ Design	Sample/ Setting	Instruments/ Methods	Results	Key Findings
Al-Dewik et al. (2016)	N =36 adult chronic myeloid leukemia (CML) patients who	• Adherence measure: MEMS, Morisky Medication Adherence	• 14.3% were non-adherent per MEMS, 16% were non-adherent per MPR, and 31% were non-adherent per MMAS,	Adherent gets higher adherence when it measured by MEMS

• **Design:** Prospective cohort study	are taking Imatinib (Mean age =42, Female=22%) in Qatar.	Scale (MMAS), MPR (MEMS ≤ 90% = nonadherent, MMAS score of ≥ 11 = good adherence, MPR ≥ 80% = high Adherence) • Other measures: electronic medical records using 2013 ELN milestones adherent and 39% nonadherent	• The MPR results revealed that 16% of patients had poor access to treatment through the hospital pharmacy.	and MPR, but not significant using MMAS
Banegas et al. (2018) • **Design:** Retrospective , secondary data analysis	• N =10,177 cancer (breast, prostate, colorectal cancer) patient who are taking statin drugs between 2000-2012 (Female 39%) • SEER, Kaiser Permanente Northern California	• Adherence measure: PDC -adherent (PDC≥0.80); partially-adherent (PDC=0.20–0.79), non-adherent (PDC<0.20) • Focused on evaluating NA on different ethnic groups	• 6.0% were non-adherent, 24.4% were partially adherent and 69.7% of all patients were adherent. • Breast cancer: lowest pre-cancer diagnosis adherence, with 67.1% adherent in both two years • Colorectal cancer (AdherentYear– 2=70.8% and AdherentYear–1=69.7%) • Prostate cancer patients (AdherentYear–2=70.8% and AdherentYear–1=70.9%). • Statin adherence decreased from pre- to post-cancer diagnosis among breast and colorectal cancer patients.	• Adherence to statins was generally higher among non-Hispanic whites.
Clarks et al. (2021) • **Design:** Retrospective	• N =2,049 chronic myeloid leukemia between Jan 2007-Dec2017 in the U.S. (Mean age =47.9, Female=46s%)	• Adherence measure: PDC using the Truven Health MarketScan Commercial and Medicare Supplemental Databases	• Average PDC = 87% • Never adherent (n = 145) • Initially non-adherent becoming adherent (n = 214) • Initially adherent becoming nonadherent (n = 181)	• Factors related with non-adherence: female gender, younger age, less concomitant medication, longer

, secondary data analysis		• PDC was chosen instead of MPR because it provides a more conservative estimate of adherence and has been endorsed by the Pharmacy Quality Alliance/National Quality Forum	• Stable adherent behavior (n = 1,509) • Factors are not related to non-adherence: Co-morbidity, financial burden, insurance type, relationship of patient to policyholder, and medication starting time	time on treatment, delayed initiation of treatment, or on a second-generation of tyrosine kinase inhibito (cancer medication)
Darkow et al. (2007) • **Design:** Retrospective analysis of data	• N =267 Patients with chronic myeloid leukaemia (CML) (taking imatinib) in the U.S.A.	• Adherence measure: Refill data from an anonymous database including electronic pharmacy records and medical claims using MPR • Focused on patient and condition-related factors • No theory utilized	• Mean MPR was 77.7%, with 31% of patients having a treatment interruption. However, all of these patients resumed imatinib within the study period. In this population • MPR was found to be inversely associated with healthcare costs excluding imatinib and medical costs	• Factors related with non-adherence: increased amount of different medication, starting with higher dose, female gender, high cancer complexity (difficulty of managing the patient because of comorbidities)
Dashputre et al. (2020) • **Design:** Retrospective analysis of data	• N =701 (Mean age= 67.1, Female =35%) and 2,385 (Mean age =63.5, Female= 44.1%) patients with chronic lymphocytic leukemia/small lymphocytic	• Adherence measure: PDC from Refill data in the IBM MarketScan Commercial Claims and Medicare Supplement databases between 2013 and 2016 (PDC ≥ 80% were considered adherent)	• PDC= 87.9 (90days), 81.8 (180days), and 78.2 (270 days), and 75.3 (365 days) for CLL/SLL • PDC= 83.3 (90 days), 69.2 (180days), 60.9 (270 days), and 57.6 for MM • Adherent patients with CLL/SLL were aged 65 years and older (vs. aged 18-64 years), resided in the Northeast U.S. (vs. the Southern), and had	• Factors related with non-adherence: younger age, increased comorbidity burden, previous cancer therapy, health insurance type, and

	lymphoma (CLL/SLL) and multiple myeloma (MM) respectively who are taking oncolytic agents	• Focused on patient healthcare system, and therapy-related factors	more emergency department visits in the baseline period.	higher outpatient visits.
De Figueierdo Jr. et al. (2014) • **Design:** prospective cohort	• N =30 breast and colorectal cancer patients who are taking capecitabine (Mean age = 60.2, Female= 40.2%) • São Paulo, Brazil	• Adherence measure: pill counting by researcher in front of patient • Other measures: the quality-of-life questionnaire QLQ-C30 at the initial visit and 8 or 12 weeks after the beginning of the treatment • Focused on patient and socioeconomic-related factors • No theory utilized	• 3.8% of breast cancer participants and 11.7% colorectal cancer patients were non-adherent • Their methods may have overestimation of adherence, since patients may conceal from the interviewer that they have disregarded some pills. • No strong correlation between medication adherence and functional or symptom scale rates had been found.	• Factors related with non-adherence: dyspnea severity
Geissler et al. (2017) • **Design:** retrospective secondary data analysis	• N =2,546 CML patients from 81 Countries (Western and Eastern Europe, Anglo American countries, Asia, Latin-America, Near and Middle East) between Sep 2012 - Jan 2013	• Adherence measure: Modified Morisky medication adherence scale for Imatinib, dasatinib, nilotinib (<6 low adherence, 6-7.75medium adherence, 8 high adherence) • Focused on patient, therapy, and	• More than 2 years since diagnosis significantly lowered chance of being highly adherent. • No significant relationship between adherence and phase of disease, taking part in a clinical trial, having a routine and information provided on the risk of nonadherence.	• Factors related with non-adherence: high personal payments, female gender, younger age, concomitant medication, not living with family or partner, side effects, more than one dose per day, medication

		socioeconomic-related factors • No theory utilized		type, less satisfaction with information from doctor
Grundmark et al. (2012) • **Design:** retrospective secondary data analysis	• N =1,406 prostate cancer patients who are taking bicalutamide (Age over 65 were 11.6%, less than 65 were 88.4%) • Sweden	• Adherence measure: pharmacy registry databases from January 1997 to December 2006, data measured by calculating the medical possession ratio using a flexible starting period (MPRf) • Focused on patient and socioeconomic-related factors • No theory utilized	• 40% of patients were non-adherent • Discontinuation reasons differed with disease severity. • Neither marital status, socio- economic status, co-morbidity according to the Charlson co-morbidity index nor the medical specialty of physician initiating the treatment had a significant impact on the adherence.	• Factors related with non-adherence: Age above 75 years and less severe disease.
Halpern et al. (2009) • **Design:** retrospective cohort	• N =465 chronic myeloid leukemia (CML) or gastrointestinal stromal tumors (GIST) patients in large national U.S. health plan data	• Adherence measure: MPR data from June 2001 to March 2005 • Focused on patient and socioeconomic-related factors • No theory utilized	• 23.4% of patients were non-adherent • Good adherence to imatinib, on average, was associated with $121,247 lower medical costs, $57,266 lower health care costs, 31.3 times fewer inpatient hospitalizations, and 9.1 times shorter LOS as compared with poor adherence.	• Patients with GIST (vs. CML) and those with higher Charlson Comorbidity Index scores had significantly higher medical and health care costs. • Good adherence to imatinib was associated with

				substantially lower follow-up medical and health care costs relative to poor adherence, controlling for condition (ie, CML or GIST) and demographic and health factors.
Hirao et al. (2017) • **Design:** cross-sectional	• N =117 (Mean age =64.5, Female=27%) gastroenterological (colorectal, gastric, pancreatic, gallbladder, GIST, liver) cancer patients • Japan	• Adherence measure: self-report • Other measures: patient's past medical histories, trust in physician scale • WHO's multi-dimensional model (FDM)	•Medication non-adherence was 43.6% for GI cancer patients. • The adherence for oral cancer medication as: XELODA= 82.6%; Nexavar =75.0%; TS-1= 62.9%; Glivec= 40.0%; and UFT =37.0%. • Patient-related (age, gender, marital status, cohabitation status), socioeconomical-related (employment status, educational status, financial leeway), condition-related time since diagnosis, type of cancer, involved in metastatic cancer, subjective symptoms like pain, Anxiety and depression), therapy-related (Cytotoxic and Molecularly target medications, total body chemotherapy, post-operative adjuvant chemotherapy, preoperative chemotherapy, # of times to take oral chemotherapy, timing of taking medications), healthcare team and system-related (place of the initial treatment such as inpatient or outpatient, trust in physician scale) related factors	• Factors related with non-adherence: worsening of symptoms, having diarrhea, experiencing pain, taking oral chemotherapy medication every 8 hour (vs. after meal) and a decreased sense of priority for medication

Klein et al. (2006) • **Design:** Quantitative study	• N =90 myelodysplastic syndromes (MDS) who are taking topotecan.	• Adherence measure: Electronic monitoring devices • No theory utilized	• Adherence did not differ in two regimens and the rate was excellent, with 90%. • Topotecan pharmacokinetics were characterized with first-order absorption and elimination. • Pharmacokinetic parameter assessments did not alter between the once a day and twice a day dosing groups. • Topotecan exposure was higher in the twice a day than once a day.	• MDS patient's oral topotecan adherence was high for both the drug is prescribed once or twice daily
Lafeuille et al. (2014) • **Design:** retrospective secondary data analysis	• Prostate cancer patients who are taking Abiraterone acetate • N =515 from dataset1 and 3,228 from dataset2 (Mean age = 72.2) in the U. S. A.	• Adherence measure: MPR data (databases—Dataset 1: Truven Health Analytics MarketScan (December 2010 to August 2012) and Dataset 2: Symphony Health Solutions' ProMetis Lx (June 2009 to March 2013). • No theory utilized	• 7 % of patients were non-adherent • Similar adherence patterns were observed for patients in different age groups, for patients with commercial health care plans versus patients with Medicare coverage, and for patients with recent chemotherapy (within 180 days before initiation of abiraterone acetate) compared with patients without.	• Patients with Medicare insurance had slightly higher adherence than having commercial health insurance. • Patients without recent chemotherapy had slightly higher adherence than patients with recent chemotherapy.
Lee & Salloum (2015)	• N =1,397 adult (older than 18 years) cancer patients in the U.S. (Less than 40 years (1124/10998=10.2%)	• Adherence measure: Using the 2006-2013 National Health Interview Survey	• Medication-NA rate was 12.70 %. •African-Americans were 2.64 times more likely (95 % confidence interval (CI), 1.73 to 4.01) and Hispanics 2.07 times more likely (95 % CI, 1.32 to 3.24) than whites to report CRN. Among younger cancer survivors, Hispanics were 1.61	Significant racial and ethnic disparities in medication NA were evident among cancer survivors. Older African-American and Hispanic overall

• **Design:** Secondary data-analysis	40-64 (5,168/10998=47%) 65-70 (3814/10998=34.7%) Older than 80 (892/10998=8.1%)		times more likely (95 % CI, 1.23 to 2.10) than whites to report medication NA.	survivors were more likely to report NA in the past year compared with non-Hispanic whites.
Marques & Pierin (2008) • **Design:** cross-sectional	• N =61 Brazil cancer patients under anti-neoplastic oral therapy (Capecitabine, Mercaptopurine, Dexamethasone, Thalidomide and hormone therapy drugs) (Mean age= 54.8, Female=64%)	• Adherence measure: Morisky and Green Test (non-adherent when it is lower than graded as 3). • Other measures: outpatient past medical histories obtained • Focused on patient and socioeconomic-related factors	• 28% of patients were non-adherent • All the patients using Temozolamide and Mercaptopurine reported the lack of health team support regarding treatment. • Concerning other drugs (Thalidomide/ Dexamethasone), patients referred to health professionals' lack of support. • Most studied patients were white, married, with higher education and performing administrative or commercial activities, followed by self-employed individuals	• Factors related with non-adherence: longer treatment time, type of medication (mercaptopurine, dexamethasone, thalidomide, and hormone therapy drugs), patients who had alternative treatment (massage), did not have radiotherapy
Mathes et al. (2014) • **Design:** systematic review (quantitative studies)	• N = 22 studies including adult patients (≥18 years) with malignant neoplasms who are taking oral anticancer agents	• Adherence measure: self-report (questionnaires such as Morisky scale, VAS, BMQ), MEMS, pill count	• Low age and very high age seem to be associated with lower adherence. • Social support, intake of aromatase inhibitors, and lower out-of-pocket costs for medication seem to have a positive effect on adherence. • Depression and the number of different medications seem to have a negative effect on adherence.	• Factors related with non-adherence: younger age (n=7), older age (n=12), ethnic status (being non-white (i.e., black) (n=2)), social support (n=3), depression (n=4),

				number of different medications (n=4), and less out of-pocket costs (n=2)
Noens et al. (2009) • **Design:** Prospective observational study	• N =169 Patients with CML in Belgium (Mean age = 57.2, Female 45 %)	• Adherence measure: Patient Visual Analog Scale (VAS) rating, Basel Assessment of Adherence Scale (less than 1 is non-adherent), pill count: other dose taken than prescribed during 90-day period • Focused on patient and socioeconomic, condition, therapy, healthcare professionals -related factors	• 85.8% of patients were non-adherent of prescribed imatinib taken. • Factors related with adherence: Knowledge of disease and treatment, more medications to be taken daily, secondary school or higher education, self-efficacy in long-term medication behavior, physicians' higher number of active patients with CML seen in the past year, median duration of the first visit with a patient newly diagnosed with CML (practicing in a university or teaching hospital, holding specialization in hematology)	• Factors related with non-adherence: Bothersome of symptoms, number of symptoms, number of adverse events, third person perceptions of adherence, higher age, longer time since CML diagnosis, living alone, male sex, longer time on imatinib, imatinib dose more than or equal to 600 mg/day, higher degrees of chronic care received, higher (self-)reported functional status and quality of life, shorter median duration of treatment follow-up visits (presumably a

				proxy of vigilance), years of physicians' professional experience
Santos et al. (2019) • **Design:** cross-sectional	• N=129 adult prostate cancer patients initiating a first oral therapy in (median age was 70 years) and 81% of patients were treated for metastatic cancer. • Comprehensive Cancer Centre François Baclesse, Caen, France.	• Adherence measure: self-report questionnaires at 1 and 3 months after treatment. • Other measures: Montreal Cognitive assessment (MoCA) tool. • Focused on patient-related factors • No theory utilized	• The researcher showed that non-adherence of oral anticancer therapy was highly related to depression • About 10 % participants were non-adherent after 1 month of treatment and 13% after 3 months. • Short-term memory can affect non-adherence among elderly population.	• Strong association between depressive symptoms and non-adherence
Streeter et al. (2011) • **Design:** Retrospective analysis of data	• N= 10,508 U.S. any cancer patients who are on any oncolytic (oral or intravenous) within the ensuing 90 days using capecitabine, imatinib, sorafenib, lenalidomide,	• Refill data extracted from administrative claims from the Wolter Kluwer Dynamic Claims Lifecycle Database (pharmacy utilization data)-abandonment rate is defined as pharmacy claim without a subsequent paid	• 10% of abandonment rate (type of non-adherence) was observed • Medicare coverage were associated with a higher abandonment rate. Claims with cost sharing greater than $500 were four times more likely to be abandoned than claims with cost sharing of $100 or less	• High cost, increased prescription activity, lower income, type of drug (imatinib, sorafenib, sunitinib, erlotinib, lapatinib compared with capecitabine)

	sunitinib, erlotinib, temozolomide, and lapatinib	claim for oncolytic within the ensuing 90 days) between 2007 and 2009. • No theory utilized		
Timmers et al. (2015) • **Design:** Multicentre prospective observational study	• N =515 62 patients (median age 63.5 years; 53 % male) in VU University Medical Center (Amsterdam, Netherlands), between October 2009 and July 2011 in 12 Dutch hospitals	• Adherence measure: Medication Event Monitoring System (MEMS: SIMpill®, Evalan, Amsterdam, Netherlands), Steady-state blood sample after 1, 2 and 4 months of treatment in those patients taking • Focused on patient and socioeconomic-related factors • No theory utilized	• Most patients (55/62, 89 %) used MEMS during the observation period. • MEMS data showed that over one-third of patients had a non-adherence rate about 5 %. • At 1 month, 21 % of patients did not take erlotinib correctly without food symptoms and stomatitis • Fatigue (91%) and rash (86%) were the common symptoms, after 1 month of treatment.	• Risk factors identified as older age, suboptimal adherence, ocular • Adherence to erlotinib is generally high due to using MEMs device and possible Hawthorne effect.

Matrix 3: Medication Adherence in Breast Cancer with OET (16 articles)

Author/Year/ Design	**Sample/ Setting**	**Instruments/ Methods**	**Results**	**Key Findings**
Ali et al. (2022)	• N=363 male breast cancer patients and 20,722 female breast	• Adherence measure: a gap of less than 90 days in-	• Non-adherent rate was 41% for male 48.1% for female.	• Men were significantly more adherent than women (p = 0.008),

• **Design:** Secondary data-analysis	cancer patients who are taking OET from 2007 to 2015 in the Surveillance, Epidemiology, and End Results (SEER)-Medicare registry. • U. S. A	between Medicare prescriptions. • Drug discontinuation: a gap of greater than 12 months in-between Medicare prescriptions. • Focused on patient-related factors • No theory utilized	• 39 male patients (10.7%) discontinued therapy, while 324 (89.3%) did not discontinue therapy. • 1849 female patients (8.9%) discontinued therapy, while 18,873 (91.1%) patients did not.	but there was no significant difference in discontinuation among men and women
Brett et al. (2016). • **Design:** cross-sectional	• N =292 women 2-4 years post breast cancer diagnosis. • Joint Aches Cohort study (JACS) (Fenlon et al, 2014) were invited to participate	• Adherence measure: Beliefs about Medicine Questionnaire (BMQ), Medical Adherence Report Scale (MARS-5)	• Non-adherent rate was 22% • 14% was intentional non-adherers and 8% was unintentional non-adherers • More than 50% participants reported that side effects had a moderate or high impact on their quality of life.	• Factors related with (intentional) non-adherence: the presence of side effects ($p<0.03$), greater concerns about medications ($p<0.001$), and a lower perceived necessity to take OET ($p<0.001$). • Factors associated with (unintentional) non-adherence: younger age (<65), ($p<0.001$), post-secondary education ($p=0.046$), and paid employment ($p=0.031$).
Fleming et al. (2022)	• N =62 articles include adult (over 18 years old) breast	• Adherence measure: self-report measures (MMAS, MARS), pill count,	• Only one study showed positive relationship between side effects (anxiety/nervousness, sleep	• No relationship between side effects and

• **Design:** A quantitative systematic review	cancer patients who were prescribed OET • Search period: no limit- September 2021.	medication chart reviews, MEMS, MPR, Gap measure from hospital records, or Medicare claims (cut off >80% mostly)	problems/ insomnia, and mood disturbance/ depression) and OET adherence. mood disturbance/depression, • Several studies found no significant relationship between OET adherence and persistence, indicating hot flashes do not seem to have an impact.	adherence/persistence mostly
Harrell et al. (2017) • **Design:** Secondary data-analysis	• N=1,587 adult breast cancer patients who are taking OET from 1998 to 2011 (Mean age =56.9). • Tennessee, U. S. A	• Adherence measure: PDC (cut off >80% mostly) from patients' electronic health records in National Cancer Institute • Focused on patient-related factors • No theory utilized	• Non-adherent rate was 49% (patients were lost to follow up or did not complete 5 years of therapy) • 52% of patients changed their medication • Switching medication can help to adhere the treatment plan	• Factors related with non-adherence: older age, side effect
Inotai et al. (2021) • **Design:** systematic review	• N =12 secondary data-analysis articles including patients with non-metastatic breast cancer who are taking OET • Spain, New Zealand, Republic of Korea, USA, China, Canada, Brazil, and Sweden.	• Adherence measure: MPR, PDC, Gap from hospital records (cut off >80% mostly) • No theory framework was reported in articles	• Adherence ranged between 52.4% and 84.8%, and between 47 and 97% over 5 years • Positive association between medication non-adherence and mortality	• Medication non-adherence are positively associated with mortality, the recurrence of breast cancer, and non-persistence.

Kimmick et al. (2015) • **Design:** cross-sectional	• N =112 breast cancer patients (post-menopausal) who are taking OET (Mean age 64). • North Carolina, U.S.A.	• Adherence measure: MMAS-8 • Other measures: symptoms (BPI-SF, BFI, MENQOL-VS, FACT-T); Self-efficacy for taking medication (modified SEAMS); Self-efficacy for communication with clinicians (PEPPI); Beliefs about Medicines (BMQ)	•58.9% reported unintentional and 33.9% reported intentional non-adherent medication-taking behaviors • 81% white; mean time from surgery 40 (SD=28) months; 49% received chemotherapy (39% including a taxane); mean time on endocrine therapy, 35 (SD=29.6) months; 82% taking an aromatase inhibitor. Intentional and unintentional non-adherent behaviors were described in 33.9% and 58.9% of participants, respectively. Multivariate analysis showed that higher self-efficacy for taking medication was associated with lower levels of unintentional (p=0.002) and intentional (p=0.004) non-adherent behaviors	• Factors related with non-adherence: the presence of symptoms (p=0.03) and lower self-efficacy for physician communication (p=0.009)
Ma et al. (2021) • **Design:** Secondary data-analysis	• N=6,045 adult breast cancer patients who are taking OET from 2007 to mid 2009 (Mean age =74.6). • SEER- Medicare, U. S. A	• Adherence measure: MPR, from hospital records (cut off >80% mostly)	• SEER covered 34.6% of the US population. • The percentage of patients who were adherent in each of the 5 years (i.e., MPR>=80%) ranged from 39.4% to 64.2%. • On average, Medicare paid US$2314 (p<0.001) more on medications for adherent beneficiaries, but US$2242 (p<0.001) less on total non-drug medical costs	• Factors related with non-adherence: Less healthcare utilization of all kinds, increased health care costs (except pharmacy cost) .
Meneveau et al. (2020) • **Design:** Secondary	• N=11,037 adult breast cancer patients who are taking OET from 2007 to 2015 (Mean age =76.5). • U. S. A	• Adherence measure: MPR, from hospital records in the SEER-Medicare whose clinical characteristics matched with the C9343 trial (cut off >80% mostly)	• Non-adherence rate: 39.4% over one year • Majority of the patients were Caucasian (89%) • Factors associated with lower initiation of AET included increasing age with a risk-ratio (RR) of 0.84 (95% CI 0.83–0.86), single marital status (RR 0.95, 95% CI 0.93–0.97), white race (RR 0.96, 95%CI 0.93–0.99), lower primary care practitioner density (RR 0.96, 95%CI 0.93–0.98),	• Factors related with non-adherence: socioeconomic factors, social determinants of health, comorbidities, lower radiation facility, substance abuse history,

data-analysis			lower radiation oncologist practitioner density (RR 0.95, 95%CI 0.92–0.97), second tumor diagnosis (RR 0.94, 95%CI 0.91–0.97), and a number of comorbid conditions	COPD history and cancer-specifics
Mohamed & Elamin, 2020 • **Design:** Secondary data-analysis	• N=172 breast cancer patients who are taking OET (Mean age 53 years) in Khartoum Oncology Hospital, Sudan between 2015 and 2016)	• Adherence measure: self-report • other measure: demographics from hospital records	• Non-adherence rate: 7% • The majority of patients were stage III (45.9%) and grade II (48%). Postmenopausal (49.4%) and premenopausal (47.7%). • Regarding hormonal receptors, about 68% were oestrogen (ER)+/progesterone (PR)+ and 23.3% were ER+/PR−. Studying adherence, almost (93%) of the studied group were ≥80% adherent to TAM and AIs. The hormonal therapy persistence mean was 27.2 ± 22.5 months	• Factors related with non-adherence: patient not poor economic status (P = .006), and the marital status “not married”
Moon et al. (2017) • **Design:** systematic review	• N =61 retrospective, prospective, cross-sectional articles including patients with non-metastatic breast cancer who are taking OET between 1998 through 2012 • North America (n=34), Europe (n=17), Japan (n=1), Taiwan (n=1), Brazil	• Adherence measure: MPR, PDC, Gap from hospital records (cut off >80% mostly) • Non-persistence was defined as gaps in treatment of 45 days (n=3), 60 days (n=8), 90 days (n=2) and 180 days (n=6).	• Most studies focused on clinical and demographic factors ==> inconsistent result • Social supports were related to increased persistence • A small amount of evidence suggested that medication beliefs were associated with adherence.	• The results from this review suggest that there are no strong predictors of OET adherence or persistence. • Factors related with non-adherence: (from reviewing high-quality studies in isolation (n=22)) older women, in black women vs. white women • Psychosocial variables were associated with

	(n=1), and New Zealand (n=1)			better adherence and persistence, but the results are currently tentative
Murphy et al. (2012) • **Design:** systematic review	• N =29 correlational articles including patients with non-metastatic breast cancer who are taking OET between 1998 through 2012	• Adherence measure: MPR, PDC, Gap from hospital records (cut off >80% mostly) • No theory utilized	• Prevalence of adherence ranged from 41–72% and discontinuation (i.e., non-persistence) ranged from 31–73%, measured at the end of 5 years of treatment • None of the studies discussed how MPR values greater than 1 or negative gap values were controlled in their analysis, and only a few reported how changes in medications were analyzed	• Factors related with non-adherence: Extremes of age (older or younger), increasing out-of-pocket costs, follow-up care with a general practitioner (vs. oncologist), higher CYP2D6 activity, switching from one form of therapy to another, treatment side effects, taking less medications at baseline, no referral to an oncologist, and later year at diagnosis
Pourcelot et al. (2018) • **Design:** cross-sectional	• N =280 early-stage breast cancer patients who are taking OET between 2010-2015. (Mean age = 59.7) • France	• Adherence measure: MMAS 4 • Other measure: self-report questionnaire for socio-demographic characteristics, turner& treatment characteristics, health status.	• Non-adherent rate was 31.4% • Having a support (from caregiver), marital status, educational level, disease severity were not significant to medication NA	• Factors related with non-adherence: > 2 medications to treat comorbidities (p = 0.003), age less than 65 years (p = 0.008), and patient management in a

				university hospital setting (p = 0.014).
Sheppard et al. (2019) • **Design:** Secondary data-analysis	• N=1,925 adult breast cancer patients who are taking OET from 1998 to 2012 (Mean age =59.5). • Michigan and Georgia, U. S. A	• Adherence measure: PDC (cut off >80% mostly) from patients' medical records and claims in Henry Ford Health System (HFHS) and Kaiser Permanente-Georgia (KPGA). • Focused on patient-related factors • No theory utilized	• Non-adherent rate was 20% • 44% had a medication gap of ≤10 days; and 24% had no medication gap days • Race and age were significant in all multivariable models • Women were without their medication for an average of 37 days	• Factors related with non-adherence: Black women than white women, younger women (25-49 years old) than older age (65-93 years old), non-HMO plan (risk of having greater out-of-pocket cost)
Tan et al. (2017) • **Design:** Retrospective secondary data-analysis	• N=428 adult breast cancer patients who received OET (average age =74.8)	• Adherence measure: MPR (cut off >80% mostly) from Medicare claims data linked with cancer registries from four Appalachian states (PA, OH, KY, and NC) in 2006–2008	• Average MPR of 0.68 in the cold spots (poor adherence area) and 0.92 in the only hot spot (good adherence area), compared to the regional average of 0.83	• Persons living in a county that belonged, to a larger degree, in a health professional shortage area were less likely to adhere to AET
Tang et al. (2018) • **Design:** cross-sectional	• N=279 adult breast cancer patients who received modified radical mastectomy or breast conserving surgery from 2010 to 2011 (Less then	• Adherence measure: MPR (cut off >80% mostly) • Focused on patient-related factors • No theory utilized	• Medication adherence rate: 100.0% (1st year), 94.3% (2nd year), 79.9% (3rd year), 52.0% (4th year), 28.7% (5th year) • Tamoxifen non-adherence (100%) is worse than AIs (letrozole, Anastrozole) (43.6%) and changing drugs (42.5%)	•Adherence getting worse with the extension of time • Tamoxifen group was the worst and

	age 35 (n=5), age 35-60 (n=54), age over 60 (n=22)). • China			anastrozole group was the best
Toivonen et al. (2020) • **Design:** systematic review (Prospective, cross-sectional, retrospective studies)	• N =68 articles which include potentially modifiable factors associated with adherence to OET among breast cancer	• Adherence measure: MEMS, MPR, PDC, physician report, and self-report. • 23% of articles utilized theory (i.e., Social cognitive theory, theory of planned behavior, Protection motivation theory)	• Adherence ranging from 25.7% to 98% • Self-efficacy (psychological factor) and positive decisional balance (attitude toward OET) were the only potentially modifiable factors (n=10) • Side effects were frequently reported to be associated with intentional non-adherence (n = 4) • Sociodemographic factors (i.e., income and insurance status) were beyond the scope of the present review, they may have impacted the potentially modifiable factors examined	• Potentially modifiable factors related with non-adherence: side effects, attitudes toward OET, psychological factors, healthcare provider-related factors, sociocultural factors, and general/quality of life factors
Yussof et al. (2020) • **Design:** systematic review	• N =26 articles which include factors associated with adherence to OET among breast cancer	• Adherence measure: MEMS, MPR, PDC, physician report, and self-report • No theory framework was reported in articles	• Mean rate of adherence at five-year for implementation phase was 66.2%, and mean persistence was 66.8% • On average, adherence decreased by 25.5% from the first to fifth year. Higher rate of adherence was observed through self-report in comparison to database or medical record • Treatment with aromatase inhibitors (AI), received chemotherapy, and prior medication use were associated with improved adherence	• Factors related with non-adherence: older age, higher comorbidity index, depression and adverse effects were associated with lower adherence • Younger age has more persistent issue

Matrix 4: Medication Adherence in Breast Cancer with Other Oncolytic Medications

Lebovits et al. (1990) • **Design:** Prospective cohort study	• N =51 breast cancer patients who are taking Cytoxan (cyclophosphamide) and/or prednisone were interviewed and assessed at five points in time over a 6-month period	• Adherence measure: self-report (Taking <90% or taking >110% of oral anticancer drugs) • No theory utilized	• 37% of those patients prescribed the drug were noncompliant with oral Cytoxan either by dosage or behaviorally, and 38% of those prescribed prednisone did the same • Two patients (3.9%) non-complied by over ingestion and under- ingestion	• Factors related with non-adherence: Treatment location (private and clinic settings rather than academic setting), lower income (and lower socioeconomic status)

APPENDIX B: Data Dictionary

Lists of Codes

1. MBSF_OTH_CC (MBSF Other Chronic Condition database)

1.1 ACP_MEDICARE
1.2. ALCO_MEDICARE
1.3.ANXI_MEDICARE
1.4. BIPL_MEDICARE
1.5. BRAINJ_MEDICARE
1.6. DEPSN_MEDICARE
1.7.DRUG_MEDICARE
1.8.EPILEP_MEDICARE
1.9. FIBRO_MEDICARE
1.10. HEARIM_MEDICARE
1.11. HEPVIRAL_MEDICARE
1.12. HIVAIDS_MEDICARE
1.13. INTDIS_MEDICARE
1.14. LEADIS_MEDICARE
1.15. LEUKLYMPH_MEDICARE
1.16. LIVER_MEDICARE
1.17. MIGRAINE_MEDICARE
1.18. MOBIMP_MEDICARE
1.19. OBESITY_MEDICARE
1.20. OUD_ANY_MEDICARE
1.21. OUD_MAT_MEDICARE
1.22. PSDS_MEDICARE
1.23. PTRA_MEDICARE
1.24. PVD_MEDICARE
1.25. SCHIOT_MEDICARE
1.26. SPIINJ_MEDICARE
1.27. TOBA_MEDICARE
1.28. ULCERS_MEDICARE
1.29. VISUAL_MEDICARE

2. MBSF_CC (MBSF Chronic Condition database)

2.1. ALZH_DEMEN
2.2. AMI
2.3. ANEMIA
2.4. ASTHMA
2.5. CHF

2.6. CHRONICKIDNEY
2.7. COPD
2.8. DIABETES
2.9. HIP_FRACTURE
2.10. HYPERL
2.11. HYPERT
2.12.HYPOTH
2.13. OSTEOPOROSIS

3. NCH_LIne (Insurance Claim Database)
3.1. LINE_COINSRNC_AMT
3.2. SERVICE_DEDUCTIBLE
3.3. CARR_LINE_PRVDR_TYPE_CD

4. PDEMTM (Medicare Part D Medication Therapy Datatbase)
4.1. CMR_PROVIDER
4.2. DRUG_THER_CHG_NUM

5. PDESAF (Medicare Part D Event and Drug Characteristics Database)
5.1. BENE_ID
5.2. BN
5.3. FILL_NUM
5.4. FRMLRY_RX_ID
5.5. DAYS_SUPLY_NUM
5.6. GNN
5.7. SRVC_DT

6. SEER_CANCER
6.1. COMBINED_SUMMARY_STAGE_2004
6.2. MARITAL_STATUS_AT_DIAGNOSIS
6.3. RACE RECODE (W, B, AI, API)
6.4. RURAL_URBAN_CONTINUUM_CODE_2003
6.5. RX SUMM-SYSTEMIC SUR SEQ
6.6. RX SUMM--SURG/RAD SEQ

1. MBSF_OTH_CC (MBSF Other Chronic Condition database)

1.1 ACP_MEDICARE

LABEL: ADHD and Other Conduct Disorders Indicator – Medicare Only Data
DESCRIPTION: This code specifies whether the enrollee met the chronic condition algorithm criteria, considering only Medicare data, for having attention deficit hyperactivity disorder (ADHD) or other conduct disorders as of the end of the calendar year.
SHORT NAME: ACP_MEDICARE
LONG NAME: ACP_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's other chronic or potentially disabling condition variables require enrollees to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Medicare Part A and Part B coverage during the entire specified time period). For ADHD and other conduct disorders, beneficiaries must have at least one inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.2. ALCO_MEDICARE

LABEL: Alcohol Use Disorders Indicator — Medicare Only Data
DESCRIPTION: This code specifies whether the enrollee met the chronic condition algorithm criteria, considering only Medicare data, for having alcohol use disorder as of the end of the calendar year.
SHORT NAME: ALCO_MEDICARE
LONG NAME: ALCO_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)

VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's other chronic or potentially disabling condition variables require enrollees to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Medicare Part A and Part B coverage during the entire specified time period). For alcohol use disorders, beneficiaries must have at least one inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.3.ANXI_MEDICARE

LABEL: Anxiety Disorders Indicator — Medicare Only Data
DESCRIPTION: This variable indicates whether the enrollee met the chronic condition algorithm criteria, considering only Medicare data, for anxiety disorders as of the end of the calendar year.
SHORT NAME: ANXI_MEDICARE
LONG NAME: ANXI_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's other chronic or potentially disabling condition variables require enrollees to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period). For anxiety disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.4. BIPL_MEDICARE

LABEL: Bipolar Disorder Indicator — Medicare Only Data

DESCRIPTION: This variable indicates whether the enrollee met the chronic condition algorithm criteria, considering only Medicare data, for bipolar disorders as of the end of the calendar year.
SHORT NAME: BIPL_MEDICARE
LONG NAME: BIPL_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's other chronic or potentially disabling condition variables require enrollees to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period). For bipolar disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.5. BRAINJ_MEDICARE

LABEL: Traumatic Brain Injury and Nonpsychotic Mental Disorders due to Brain Damage End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for traumatic brain injury and nonpsychotic mental disorders as of the end of the calendar year.
SHORT NAME: BRAINJ_MEDICARE
LONG NAME: BRAINJ_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred

within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For traumatic brain injury and nonpsychotic mental disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.6. DEPSN_MEDICARE

LABEL: Major Depressive Affective Disorder End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for major depressive affective disorder as of the end of the calendar year.
SHORT NAME: DEPSN_MEDICARE
LONG NAME: DEPSN_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For major depressive affective disorder, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.
NOTE: This depressive affective disorder condition definition is slightly different than the CCW depression condition; this depressive affective disorder condition was specified by CMS to enhance research of the Medicare-Medicaid dually enrolled population.

1.7.DRUG_MEDICARE

LABEL: Drug Use Disorder End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for drug use disorder as of the end of the calendar year.

SHORT NAME: DRUG_MEDICARE
LONG NAME: DRUG_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For drug use disorder, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.8. EPILEP_MEDICARE

LABEL: Drug Use Disorder End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for drug use disorder as of the end of the calendar year.
SHORT NAME: DRUG_MEDICARE
LONG NAME: DRUG_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For drug use disorder, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.9. FIBRO_MEDICARE

LABEL: Fibromyalgia, Chronic Pain and Fatigue End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for fibromyalgia, chronic pain, and fatigue as of the end of the calendar year.
SHORT NAME: FIBRO_MEDICARE
LONG NAME: FIBRO_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For fibromyalgia, chronic pain and fatigue, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.10. HEARIM_MEDICARE

LABEL: Sensory — Deafness and Hearing Impairment End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for a sensory (deafness and hearing) impairment as of the end of the calendar year.
SHORT NAME: HEARIM_MEDICARE
LONG NAME: HEARIM_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage

2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For sensory (deafness and hearing) impairment, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.11. HEPVIRAL_MEDICARE

LABEL: Viral Hepatitis (General) End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for viral hepatitis (general) as of the end of the calendar year.
SHORT NAME: HEPVIRAL_MEDICARE
LONG NAME: HEPVIRAL_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For viral hepatitis (general), beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.12. HIVAIDS_MEDICARE

LABEL: Human Immunodeficiency Virus and/or Acquired Immunodeficiency Syndrome (HIV/AIDS) End-of-Year Indicator — Medicare Only Claims

DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for human immunodeficiency virus and/or acquired immunodeficiency syndrome (HIV/AIDS) as of the end of the calendar year.
SHORT NAME: HIVAIDS_MEDICARE
LONG NAME: HIVAIDS_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For human immunodeficiency virus and/or acquired immunodeficiency syndrome (HIV/AIDS), beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.13. INTDIS_MEDICARE

LABEL: Intellectual Disabilities and Related Conditions End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for intellectual disabilities and related conditions as of the end of the calendar year.
SHORT NAME: INTDIS_MEDICARE
LONG NAME: INTDIS_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred

within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For intellectual disabilities and related conditions, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.14. LEADIS_MEDICARE

LABEL: Learning Disabilities End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for learning disabilities as of the end of the calendar year.
SHORT NAME: LEADIS_MEDICARE
LONG NAME: LEADIS_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For learning disabilities, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.15. LEUKLYMPH_MEDICARE

LABEL: Leukemias and Lymphomas End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for leukemias and lymphomas as of the end of the calendar year.
SHORT NAME: LEUKLYMPH_MEDICARE
LONG NAME: LEUKLYMPH_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)

VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For leukemias and lymphomas, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.16. LIVER_MEDICARE

LABEL: Liver Disease, Cirrhosis and Other Liver Conditions (excluding Hepatitis) End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for liver disease, cirrhosis, and other liver conditions (excluding hepatitis) as of the end of the calendar year.
SHORT NAME: LIVER_MEDICARE
LONG NAME: LIVER_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For liver disease, cirrhosis, and other liver conditions (excluding hepatitis), beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.17. MIGRAINE_MEDICARE

LABEL: Migraine and other Chronic Headache End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for migraine and other chronic headache as of the end of the calendar year.
SHORT NAME: MIGRAINE_MEDICARE
LONG NAME: MIGRAINE_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For migraine and other chronic headache, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.18. MOBIMP_MEDICARE

LABEL: Mobility Impairments End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for mobility impairments as of the end of the calendar year.
SHORT NAME: MOBIMP_MEDICARE
LONG NAME: MOBIMP_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage

COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For mobility impairments, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.19. OBESITY_MEDICARE

LABEL: Obesity End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for obesity as of the end of the calendar year.
SHORT NAME: OBESITY_MEDICARE
LONG NAME: OBESITY_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For obesity, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.20. OUD_ANY_MEDICARE
LABEL: Overarching OUD Disorder (Any of the Three Sub-Indicators) — Medicare Only Claims
DESCRIPTION: This variable is the Overarching Opioid Use Disorder (OUD) indicator, which identifies whether a beneficiary met any of the three opioid-related sub-Indicators as of the end of the calendar year. Beneficiaries who were identified as meeting the criteria for any of the following, also meet the criteria for this overarching indicator: OUD_DX_MEDICARE, OUD_HOSP_MEDICARE, or OUD_MAT_MEDICARE.

SHORT NAME: OUD_ANY_MEDICARE
LONG NAME: OUD_ANY_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For the overarching opioid use disorder indicator, beneficiaries must have met the criteria for at least one of the three opioid-use disorder sub-category conditions:
Diagnosis and Procedure Basis for

1.21. OUD_MAT_MEDICARE
LABEL: Use of Medication-Assisted Treatment (MAT) — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the criteria for the Use of Medication-Assisted Treatment (MAT) as of the end of the calendar year.
SHORT NAME: OUD_MAT_MEDICARE
LONG NAME: OUD_MAT _MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For use of Medication-Assisted Treatment (MAT), beneficiaries must have one or more drug claim (Medicare Part B, Medicare Part D, and/or Medicaid) with an NDC (national drug code) for opioid-MAT or one or more non-drug claim (Medicare Part B or Medicaid non-drug claim) with a HCPCs code during the two-year period.

1.22. PSDS_MEDICARE

LABEL: Personality Disorders End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for personality disorders as of the end of the calendar year.
SHORT NAME: PSDS_MEDICARE
LONG NAME: PSDS_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For personality disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.23. PTRA_MEDICARE

LABEL: Post-Traumatic Stress Disorder End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for post-traumatic stress disorder as of the end of the calendar year.
SHORT NAME: PTRA_MEDICARE
LONG NAME: PTRA_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage

COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For post-traumatic stress disorder, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.24. PVD_MEDICARE

LABEL: Peripheral Vascular Disease End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for peripheral vascular disease as of the end of the calendar year.
SHORT NAME: PVD_MEDICARE
LONG NAME: PVD_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For peripheral vascular disease, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.25. SCHIOT_MEDICARE

LABEL: Schizophrenia and Other Psychotic Disorders End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for schizophrenia and other psychotic disorders as of the end of the calendar year.
SHORT NAME: SCHIOT_MEDICARE

LONG NAME: SCHIOT_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For schizophrenia and other psychotic disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.26. SPIINJ_MEDICARE

LABEL: Spinal Cord Injury End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for spinal cord injury as of the end of the calendar year.
SHORT NAME: SPIINJ_MEDICARE
LONG NAME: SPIINJ_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For spinal cord injury, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.27. TOBA_MEDICARE

LABEL: Tobacco Use Disorders End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for tobacco use disorders as of the end of the calendar year.
SHORT NAME: TOBA_MEDICARE
LONG NAME: TOBA_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For tobacco use disorders, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.28. ULCERS_MEDICARE

LABEL: Pressure Ulcers and Chronic Ulcers End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for pressure ulcers and chronic ulcers as of the end of the calendar year.
SHORT NAME: ULCERS_MEDICARE
LONG NAME: ULCERS_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage

3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For pressure ulcers and chronic ulcers, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

1.29. VISUAL_MEDICARE

LABEL: Sensory — Blindness and Visual Impairment End-of-Year Indicator — Medicare Only Claims
DESCRIPTION: This variable indicates whether a beneficiary met the condition criteria for sensory (blindness and visual) impairment as of the end of the calendar year.
SHORT NAME: VISUAL_MEDICARE
LONG NAME: VISUAL_MEDICARE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The condition variable requires beneficiaries to satisfy both claims criteria (a minimum number/type of Medicare claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (Medicare FFS Part A and Part B coverage during the entire specified time period).
For sensory (blindness and visual) impairment, beneficiaries must have at least one Medicare inpatient claim or two other non-drug claims of any service type with a related code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

2. MBSF_CC (MBSF Chronic Condtion database)

2.1. ALZH_DEMEN

LABEL: Alzheimer's Disease and Related Disorders or Senile Dementia End-of-Year Indicator

DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for Alzheimer's disease and related disorders or senile dementia as of the end of the calendar year.
SHORT NAME: ALZHDMTA
LONG NAME: ALZH_DEMEN
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For Alzheimer's disease and related disorders or senile dementia, beneficiaries must have at least one inpatient, SNF, home health, Part B institutional, or Part B non-institutional (carrier) claim with a related code in any position during the three-year reference period.

2.2. AMI

LABEL: Acute Myocardial Infarction End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for an acute myocardial infarction (AMI; heart attack) as of the end of the calendar year.
SHORT NAME: AMI
LONG NAME: AMI
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and

occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For heart attack, beneficiaries must have at least one inpatient claim with a heart attack diagnosis code in the first or second position during the one-year reference period.

2.3. ANEMIA

LABEL: Anemia End Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for anemia as of the end of the calendar year.
SHORT NAME: ANEMIA
LONG NAME: ANEMIA
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For anemia, beneficiaries must have at least one inpatient, SNF, home health, Part B institutional, or Part B non-institutional (carrier) claim with an anemia code in any position during the one-year reference period.

2.4. ASTHMA

LABEL: Asthma End Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for asthma as of the end of the calendar year.
SHORT NAME: ASTHMA
LONG NAME: ASTHMA
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage

1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For asthma, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims with an asthma code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

2.5. CHF

LABEL: Heart Failure End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for congestive heart failure (CHF) as of the end of the calendar year.
SHORT NAME: CHF
LONG NAME: CHF
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For congestive heart failure, beneficiaries must have at least one inpatient or Part B (institutional or non-institutional) claim with a heart failure code in any position during the two-year reference period.

2.6. CHRONICKIDNEY

LABEL: Chronic Kidney Disease End-of-Year Indicator

DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for chronic kidney disease (CKD) as of the end of the calendar year.
SHORT NAME: CHRNKIDN
LONG NAME: CHRONICKIDNEY
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For chronic kidney disease, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims with a chronic kidney disease code in any position during the two-year reference period. When two claims are required, they must occur at least one day apart.

2.7. COPD

LABEL: Chronic Obstructive Pulmonary Disease End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for chronic obstructive pulmonary disease (COPD) and bronchiectasis as of the end of the calendar year.
SHORT NAME: COPD
LONG NAME: COPD
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and

occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For COPD and bronchiectasis, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims with a COPD code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

2.8. DIABETES

LABEL: Diabetes End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for diabetes as of the end of the calendar year.
SHORT NAME: DIABETES
LONG NAME: DIABETES
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For depression, beneficiaries must have at least one inpatient, SNF, home health, or Part B (institutional or non-institutional) claim with a depression code in any position during the one-year reference period.

2.9. HIP_FRACTURE

LABEL: Hip/Pelvic Fracture End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for a hip/pelvic fracture as of the end of the calendar year.
SHORT NAME: HIPFRAC
LONG NAME: HIP_FRACTURE
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)

VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For hip/pelvic fractures, beneficiaries must have at least one inpatient or SNF claim with a hip/pelvic fracture code in any position during the one-year reference period.

2.10. HYPERL

LABEL: Hyperlipidemia End Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for hyperlipidemia as of the end of the calendar year.
SHORT NAME: HYPERL
LONG NAME: HYPERL
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For hyperlipidemia, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims, with a hyperlipidemia code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

2.11. HYPERT

LABEL: Hypertension End Year Indicator

DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for hypertension (high blood pressure) as of the end of the calendar year.
SHORT NAME: HYPERT
LONG NAME: HYPERT
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For hypertension, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims, with a hypertension code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

2.12.HYPOTH

LABEL: Acquired Hypothyroidism End Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for acquired hypothyroidism as of the end of the calendar year.
SHORT NAME: HYPOTH
LONG NAME: HYPOTH
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and

occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For acquired hypothyroidism, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims with an acquired hypothyroidism code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

2.13. OSTEOPOROSIS

LABEL: Osteoporosis End-of-Year Indicator
DESCRIPTION: This variable indicates whether a beneficiary met the Chronic Condition Warehouse (CCW) criteria for osteoporosis as of the end of the calendar year.
SHORT NAME: OSTEOPRS
LONG NAME: OSTEOPOROSIS
TYPE: NUM
LENGTH: 1
SOURCE: CCW (derived)
VALUES: 0 = Beneficiary did not meet claims criteria or have sufficient fee-for-service (FFS) coverage
1 = Beneficiary met claims criteria but did not have sufficient FFS coverage
2 = Beneficiary did not meet claims criteria but had sufficient FFS coverage
3 = Beneficiary met claims criteria and had sufficient FFS coverage
COMMENT: The CCW's chronic condition flags require beneficiaries to satisfy both claims criteria (a minimum number/type of claims that have the proper diagnosis codes and occurred within a specified time period) and coverage criteria (FFS Part A and Part B coverage during the entire specified time period).
For osteoporosis, beneficiaries must have at least one inpatient, SNF, or home health claim, or two-Part B (institutional or non-institutional) claims, with an osteoporosis code in any position during the one-year reference period. When two claims are required, they must occur at least one day apart.

3. NCH_LIne (Insurance Claim Database)

3.1. LINE_COINSRNC_AMT

LABEL: Line Beneficiary Coinsurance Amount
DESCRIPTION: The beneficiary coinsurance liability amount for this line-item service on the non-institutional claim.
This variable is the beneficiary's liability for coinsurance for the service on the line-item record.

Beneficiaries only face coinsurance once they have satisfied Part B's annual deductible, which applies to both institutional (e.g., Hospital Outpatient) and non-institutional (e.g., Carrier and DME) services.
For most Part B services, coinsurance equals 20 percent of the allowed amount.
SHORT NAME: COINAMT
LONG NAME: LINE_COINSRNC_AMT
TYPE: NUM
LENGTH: 12
SOURCE: NCH
VALUES: XXX.XX
COMMENT: Medicare payments are described in detail in a series called the Medicare Learning Network (MLN) "Payment System Fact Sheet Series" (reference the list of MLN publications at: http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/MLN-Publications.html).

3.2. SERVICE_DEDUCTIBLE
LABEL: Line Service Deductible Indicator Switch
DESCRIPTION: Switch indicating whether or not the line-item service on the non-institutional claim is subject to a deductible.
SHORT NAME: DED_SW
LONG NAME: LINE_SERVICE_DEDUCTIBLE
TYPE: CHAR
LENGTH: 1
SOURCE: NCH
VALUES: 0 = Service Subject to Deductible
1 = Service Not Subject to Deductible

3.3. CARR_LINE_PRVDR_TYPE_CD
LABEL: Carrier Line Provider Type Code
DESCRIPTION: Code identifying the type of provider furnishing the service for this line item on the carrier claim.
SHORT NAME: PRV_TYPE
LONG NAME: CARR_LINE_PRVDR_TYPE_CD
TYPE: CHAR
LENGTH: 1
SOURCE: NCH
VALUES: For Physician/Supplier Claims:
0 = Clinics, groups, associations, partnerships, or other entities
1 = Physicians or suppliers reporting as solo practitioners
2 = Suppliers (other than sole proprietorship)

3 = Institutional provider
4 = Independent laboratories
5 = Clinics (multiple specialties)
6 = Groups (single specialty)
7 = Other entities
COMMENT: PRIOR TO VERSION H, DME claims also used this code; the following were valid codes:
0 = Clinics, groups, associations, partnerships, or other entities for whom the carrier's own ID number has been assigned.
1 = Physicians or suppliers billing as solo practitioners for whom SSN's are shown in the physician ID code field.
2 = Physicians or suppliers billing as solo practitioners for whom the carrier's own physician ID code is shown.
3 = Suppliers (other than sole proprietorship) for whom EI numbers are used in coding the ID field.
4 = Suppliers (other than sole proprietorship) for whom the carrier's own code has been shown.
5 = Institutional providers and independent laboratories for whom EI numbers are used in coding the ID field.
6 = Institutional providers and independent laboratories for whom the carrier's own ID number is shown.
7 = Clinics, groups, associations, or partnerships for whom EI numbers are used in coding the ID field.
8 = Other entities for whom EI numbers are used in coding the ID field or proprietorship for whom EI numbers are used in coding the ID field.

4. PDEMTM (Medicare Part D Medication Therapy Datatbase)

4.1. CMR_PROVIDER

LABEL: Comprehensive Medication Review (CMR) provider type
DESCRIPTION: This variable indicates the type of qualified provider who performed the initial comprehensive medication review (CMR)
TYPE: CHAR
LENGTH: 2
SOURCE: CMS (HPMS files)
VALUES: 01 = Physician
02 = Registered Nurse
03 = Licensed Practical Nurse

04 = Nurse Practitioner
05 = Physician's Assistant
06 = Local Pharmacist
07 = LTC Consultant Pharmacist
08 = Plan Sponsor Pharmacist
09 = Plan Benefit Manager (PBM) Pharmacist
10 = MTM Vendor Local Pharmacist
11 = MTM Vendor In-house Pharmacist
12 = Hospital Pharmacist
13 = Pharmacist — other
14 = Supervised pharmacy intern (new in 2016)
99 = Other
Null/missing = beneficiary did not receive a CMR
COMMENT: CMS created the MTM file from information submitted by Part D plan sponsors to CMS's Health Plan Management System (HPMS).
If more than one CMR is received, this applies to the initial CMR.

4.2. DRUG_THER_CHG_NUM

LABEL: Number of drug therapy problem resolutions with prescribers
DESCRIPTION: This variable indicates the number of drug therapy problem resolutions with prescribers resulting from recommendations made to beneficiary's prescriber(s) as a result of Medication Therapy Management (MTM) services
TYPE: NUM
LENGTH: 8
SOURCE: CMS (HPMS files)
VALUES: 0–xx
COMMENT: CMS created the MTM file from information submitted by Part D plan sponsors to CMS's Health Plan Management System (HPMS).

5. PDESAF (Medicare Part D Event and Drug Characteristics Database)

5.1. BENE_ID

LABEL: CCW Encrypted Beneficiary ID Number
DESCRIPTION: The unique CCW identifier for a beneficiary.
The CCW assigns a unique beneficiary identification number to each individual who receives Medicare and/or Medicaid, and uses that number to identify an individual's records in all CCW data files (e.g., Medicare claims, MAX claims, MDS assessment data).

This number does not change during a beneficiary's lifetime and each number is used only once.
The BENE_ID is specific to the CCW and is not applicable to any other identification system or data source.
SHORT NAME: BENE_ID
LONG NAME: BENE_ID
TYPE: CHAR
LENGTH: 15
SOURCE: CCW
VALUES: —
COMMENT: —

5.2. BN

LABEL: Brand Name
DESCRIPTION: This is the brand name of the dispensed PDE, according to the First DataBank (FDB) reference files.
The name that appears on the package label provided by the manufacturer.
When this variable appears in the Formulary file, it is the FDB brand name for a drug product on the formulary.
SHORT NAME: BN
LONG NAME: BN
TYPE: CHAR
LENGTH: 30
SOURCE: First DataBank
VALUES: text description; DIABETIC SUPPLY for all diabetic supplies
COMMENT: In the PDE file, this variable is populated by linking to the proprietary First DataBank MedKnowledge database by matching on the National Drug Code (NDC; variable in the PDE files called the product service identifier PROD_SRVC_ID).
In the Formulary file, this variable is populated by matching the drug products on the Part D Plan submitted formulary to FDB. Part D plan sponsors submit the formulary to the CMS Health Plan Management System (HPMS). Plans identify the drug products on their formularies using the National Library of Medicine RxNorm Concept Unique Identifiers (RXCUIs). Each RXCUI corresponds to a unique brand name and clinical formulation (same ingredients, strength, and dosage form).

5.3. FILL_NUM

LABEL: Number of drug fills
DESCRIPTION: This field indicates the number fill of the current dispensed supply.

SHORT NAME: FILL_NUM
LONG NAME: FILL_NUM
TYPE: NUM
LENGTH: 3
SOURCE: PDE
VALUES: Possible values are 0–99
COMMENT: The number of days of a drug that are supplied vary considerably across PDEs.

5.4. FRMLRY_RX_ID

LABEL: Formulary identification number
DESCRIPTION: This variable is the unique identification number assigned to each formulary. Part D plans submit their formularies to CMS and identify the drug products that are covered using the National Library of Medicine's RxNorm Concept Unique Identifiers (RXCUIs).
The same formulary may be used by more than one plan benefit package (PBP) within a contract.
SHORT NAME: FORMULARY_ID
LONG NAME: FORMULARY_ID
TYPE: CHAR
LENGTH: 8
SOURCE: PDE and CMS HPMS (derived)
VALUES: 8-digit numeric value
COMMENT: The CCW constructs a Formulary Characteristics File from the CMS Approved Formulary Data found in the CMS's Health Plan Management System (HPMS). This variable is first available in 2010. This variable was always encrypted from 2010–2012 to comply with CMS privacy rules.

5.5. DAYS_SUPLY_NUM

LABEL: Days Supply
DESCRIPTION: This field indicates the number of days' supply of medication dispensed by the pharmacy and consists of the amount the pharmacy enters for the prescription.
SHORT NAME: DAYSSPLY
LONG NAME: DAYS_SUPLY_NUM
TYPE: NUM
LENGTH: 3
SOURCE: PDE
VALUES: Possible values are 0–999.

COMMENT: CMS accepts blanks in PDEs where NON-STANDARD FORMAT CODE IS B, X, or P.

5.6. GNN

LABEL: Generic Name
DESCRIPTION: This is the generic name of the dispensed PDE, according to the First DataBank (FDB) reference files. It is the drug ingredient name adopted by United States Adopted Names (USAN).
When this variable appears in the Formulary file, it is the FDB generic name for a drug product on the formulary.
SHORT NAME: GNN
LONG NAME: GNN
TYPE: CHAR
LENGTH: 30
SOURCE: First DataBank
VALUES: text description of drug (e.g., RISEDRONATE SODIUM, MEMANTINE HCL)
COMMENT: FDB uses the chemical name when the USAN name is not available. For multi-ingredient products, abbreviations may be used (e.g., HCTZ [Hydrochlorothiazide] and PP [Phenylpropanolamine]).
In the Formulary file, this variable is populated by matching the drug products on the Part D Plan submitted formulary to FDB. Part D plan sponsors submit the formulary to the CMS Health Plan Management System (HPMS). Plans identify the drug products on their formularies using the National Library of Medicine RxNorm Concept Unique Identifiers (RXCUIs). Each RXCUI corresponds to a unique brand name and clinical formulation (same ingredients, strength, and dosage form).
In the PDE file, this variable is populated by linking to the proprietary First DataBank MedKnowledge database by matching on the National Drug Code (NDC; variable in the PDE files called the product service identifier PROD_SRVC_ID).

5.7. SRVC_DT

LABEL: RX Service Date
DESCRIPTION: This field contains the date on which the prescription was filled.
SHORT NAME: SRVC_DT
LONG NAME: SRVC_DT
TYPE: DATE
LENGTH: 8
SOURCE: PDE
VALUES: Date formatted as CCYYMMDD

COMMENT: —

6. SEER_CANCER

6.1. COMBINED_SUMMARY_STAGE_2004

NAACCR Item #: N/A
SAS Variable Name: Combined_Summary_Stage_2004
Research Plus Limited-Field: Yes
Field Description: Combined Summary Stage field to facilitate stage analyses over time. Created from SEER Combined Summary Stage 2000 (2004-2017) & Derived Summary Stage 2018 (2018+). For more information including sites, years and registries for which it isn't calculated, see https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/

SUMMARY STAGE
0 In situ, intraepithelial, noninvasive (Stage 0)
• In situ: noninfiltrating; intraepithelial
• Intraductal WITHOUT infiltration
• Lobular neoplasia, grade 3 (LIN 3)
• Paget disease, in situ
1 Localized only (localized, NOS) (Stage I)
• Confined to breast tissue and fat including nipple and/or areola
• Paget disease WITH or WITHOUT underlying tumor
2 Regional by direct extension only (Stage II)
• Attachment or fixation to pectoral muscle(s) or underlying tumor
• Chest wall
• Deep fixation
• Extensive skin involvement WITH or WITHOUT dermal lymphatic filtration o Edema of skin
o En cuirasse
o Erythema
o Inflammation of skin
3 Regional lymph node(s) involved only (Stage II)
• Axillary, NOS (ipsilateral) o Level I (low-axilla) (low) (superficial), NOS [adjacent to tail of breast] Anterior (pectoral)
Lateral (brachial)
Posterior (subscapular)
o Level II (mid-axilla) (central), NOS Interpectoral (Rotter's)
o Level III (high) (deep), NOS Apical (subclavian)
Axillary vein

• Fixed/matted axillary (level I and II) (ipsilateral)
• Infraclavicular (subclavicular) (ipsilateral)
• Internal mammary (parasternal) (ipsilateral)
• Intramammary (ipsilateral)
• Regional lymph node(s), NOS o Lymph node(s), NOS
4 Regional by BOTH direct extension AND regional lymph node(s) involved (Stage II)
• Codes (2) + (3)
7 Distant site(s)/lymph node(s) involved (Stage III)
• Distant site(s) (including further contiguous extension) o Adrenal (suprarenal) gland
o Bone, including contralateral ribs
o Contralateral (opposite) breast-if stated as metastatic
o Ipsilateral rib(s) (discontiguous extension only, see code 2 for contiguous extension)
o Lung
o Ovary
o Satellite nodule(s) in skin other than primary breast
o Skin over Axilla
Contralateral (opposite) breast
Sternum
Upper abdomen
• Distant lymph node(s), NOS o Axillary (contralateral or bilateral)
o Cervical, NOS
o Fixed/matted axillary (level I and II) (contralateral or bilateral)
o Infraclavicular (subclavicular) (contralateral or bilateral)
o Internal mammary (parasternal) (contralateral or bilateral)
o Intramammary (parasternal) (contralateral or bilateral) f
o Supraclavicular (transverse cervical) (ipsilateral, contralateral or bilateral)
• Distant metastasis, NOS o Carcinomatosis
o Distant metastasis WITH or WITHOUT distant lymph node(s)
9 Unknown if extension or metastasis (STAGE IV)

6.2. MARITAL_STATUS_AT_DIAGNOSIS

NAACCR Item #: 150
SAS Variable Name: Marital_status_at_diagnosis
Research Plus Limited-Field: No
Field Description: This data item identifies the patient's marital status at the time of diagnosis for the reportable tumor.

Code	Description
1	Single (never married)
2	Married (including common law)
3	Separated
4	Divorced
5	Widowed
6	Unmarried or domestic partner (same sex or opposite sex or unregistered)
9	Unknown
14	Blank

6.3. RACE RECODE (W, B, AI, API)

NAACCR Item #: N/A

SAS Variable Name: Race_recode_W_B_AI_API
Research Plus Limited-Field: Yes
Field Description: Caution should be exercised when using this variable. For more information, see http://seer.cancer.gov/seerstat/variables/seer/race_ethnicity.

Code	Description
1	White
2	Black
3	American Indian/Alaska Native
4	Asian or Pacific Islander
7	Other unspecified (1991+)
9	Unknown

6.4. RURAL_URBAN_CONTINUUM_CODE_2003

NAACCR Item #: 3310
SAS Variable Name: Rural_Urban_Continuum_Code_2003
Research Plus Limited-Field: Yes

Field Description: The Rural-Urban Continuum (2003) codes (usually known as the Beale Codes) separate counties into four metropolitan and six non-metropolitan categories, based on the size their populations and form a classification scheme that distinguishes metropolitan counties by size and non-metropolitan counties by degree of urbanization and proximity to metro areas. These codes can be derived electronically, using patients' state and county at diagnosis, so registrars do not need to provide them. FIPS state and county code mappings to Beale Codes can be obtained in an Excel file at http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx

Metropolitan Counties (01-03)

	Description
	Counties in metro areas of 1 million population or more
	Counties in metro areas of 250,000 to 1 million population
	Counties in metro areas of fewer than 250,000 population

Nonmetropolitan Counties (04-09)

Code	**Description**
	Urban population of 20,000 or more, adjacent to a metro area
	Urban population of 20,000 or more, not adjacent to a metro area
	Urban population of 2,500 to 19,999, adjacent to a metro area
	Urban population of 2,500 to 19,999, not adjacent to a metro area
	Completely rural or less than 2,500 urban population, adjacent to a metro area
	Completely rural or less than 2,500 urban population, not adjacent to a metro area

	but: (Program run, but: (1) area is not included in Rural-Urban Continuum code table, or (2) record is for resident outside of state of reporting institution
	Unknown
	Program not run; record not coded

6.5. RX SUMM-SYSTEMIC SUR SEQ

NAACCR Item #: 1639
SAS Variable Name: RX_Summ_Systemic_Sur_Seq
Research Plus Limited-Field: No
Field Description: This data item records the sequencing of systemic therapy and surgical procedures given as part of first course of treatment.

Code	Description
0	No systemic therapy and/or surgical procedures; unknown if surgery and/or systemic therapy given
2	Systemic therapy before surgery
3	Systemic therapy after surgery
4	Systemic therapy both before and after surgery
5	Intraoperative systemic therapy
6	Intraoperative systemic therapy with other therapy administered before and/or after surgery
7	Surgery both before and after systemic therapy
9	Sequence unknown, but both surgery and systemic therapy given

6.6. RX SUMM--SURG/RAD SEQ

NAACCR Item #: 1380
SAS Variable Name: RX_Summ_Surg_Rad_Seq
Research Plus Limited-Field: No
Field Description: This field records the order in which surgery and radiation therapies were administered for those patients who had both surgery and radiation.

Code	Description
0	No radiation and/or surgery as defined above
2	Radiation before surgery
3	Radiation after surgery
4	Radiation both before and after surgery
5	Intraoperative radiation
6	Intraoperative radiation with other radiation given before and/or after surgery
7	Surgery both before and after radiation
9	Sequence unknown, but both surgery and radiation were given

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VITA

Sunny Yoo Ruggeri was born in Cheon-An, South Korea, in 1987 to Jiyoung Yoo and Jung Sook Kim. She constantly desired to be a great scientist. So, she started her passion for learning physics with a bachelor's degree to better understand all the tools of science. After, she graduated with a Bachelor of Science degree in Physics at Sung Kyun Kwan University, South Korea, in 2009. She continued her studies further to the graduate level focusing on Physics and Biochemistry and retrieved her Master's degree in Energy Science from the same school in 2014. During her Master's years, she worked on laser physics by using optical spectroscopy to understand photosynthesis mechanisms. She also developed a new device to increase the sensitivity of sample yield on the receiving device at Lund University, Sweden.

When Ms. Sunny Ruggeri moved to the USA, she wanted to do something more emotionally rewarding, so she changed her career to nursing. She earned her registered nurse license after graduating from the Bridgeport Hospital School of Nursing in CT, USA, in 2016. She began her career as a medical-surgical nurse at Bridgeport Hospital, Yale New Haven's satellite location in CT, USA. Ms. Ruggeri additionally obtained a degree of a Master of Science in Nursing degree in 2019. She started her nursing education career at Becker College, Worcester, MA, USA, in 2019 as a lecturer and clinical instructor. Ms. Ruggeri began working for Worcester State University as a Tenure Track Assistant Professor in 2022. She presented her Ph.D. study at the Eastern Nursing Research Society (ENRS) Conference 2021, the Oncology Nursing Society (ONS) Conference 2021, and North American Nursing Diagnosis Association (NANDA) International Conference 2023. Overall,

Ms. Ruggeri has been involved in and presented eight poster presentations and five publications in highly recognized Science Citation Index (SCI) journals.

In the Summer of 2019, Ms. Ruggeri began coursework for her Doctor of Philosophy degree in Nursing at the University of Missouri-Kansas City. She passed her comprehensive exam in February 2022. Ms. Ruggeri plans to continue with big-data analysis projects to identify the medication adherence rate and the multi-level determinants influencing medication adherence among older women with breast cancer in large samples across diverse backgrounds using the SEER-Medicare dataset.

Ms. Ruggeri is a member of the Oncology Nursing Society, the Boston Oncology Nursing Society, Eastern Nursing Research Society, and the Lambda Phi Chapter of Sigma Theta Tau International.